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CIATE TRAINING PROGRAMS

THE

Medical and Biological Sciences

at the

National Institutes of Health

1974 CATALOG

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NIH ASSOCIATE TRAINING PROGRAM
1974 Schedule

April 5	Deadline for receipt at NIH of completed applicati (Early commissioning applications are requested by F ruary 1.)
June 10-21	Interview period at NIH campus, Bethesda, Maryland. invitation only.)
July 8-23	Notification to applicants.

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FOREWORD

The National Institutes of Health conducts and supports research to find better ways of preventing or curing disease and lengthening life. In pursuit of that mission, NIH provides broad support for biomedical research, research training, and construction of research facilities in the Nation's medical and dental schools, universities, and other research centers. This is the NIH extramural program.

NIH conducts laboratory and clinical research in its own facilities on its 306-acre campus in Bethesda, Md. For example, in the past year, over 4,500 patients were admitted for investigative studies in the Clinical Center—a research hospital with 511 patient beds and 1,100 laboratories. At any point in time, more than 1,400 research projects are in progress here on the Bethesda campus and at field offices directed from here. This is the NIH intramural program.

Of the 2,319 NIH staff members with doctorates, more than 1,000 have M.D. degrees, 1,021 have Ph. D. degrees, and some have both; 100 have D.D.S. degrees and 63 have D.V.M. degrees. These individuals with their 3,800 scientifically trained assistants, represent most of the disciplines that contribute to new medical knowledge.

In this scientific community, many opportunities for professional development are available to physicians and others who are undertaking careers in medical or related research, or in academic medicine. The purpose of this catalog is to set forth in one place brief descriptions of programs of concern to those interested in Associateships at the NIH.

Roger L. Black, M.D.
Associate Director
The Clinical Center

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PART ONE

General Characteristics of Associateships

UNUSUAL opportunities for training and experience in clinical and laboratory investigation are available to physicians and dentists who receive appointments as Clinical, Research, and Staff Associates at the National Institutes of Health. These positions provide broad opportunities for career development in most of the health specialties as well as the basic science disciplines.

Appointments to the Associate Training Program are based on intellectual attainment and demonstrated research interest and ability. An individual's background in research is often a decisive factor in making selections. This applies more significantly in certain areas—such as internal medicine and psychiatry—than in others—such as surgery and radiology. Selections are made through a matching process, explained on p. 8.

Each Associate participates in a research program under the direction of his preceptor. Preceptors are staff members who give generously of their time to help the Associate—not only in relation to research problems under investigation, but in any way they can to enrich the experience of the Associate during his stay at NIH. The levels of research responsibility and latitude given to an Associate depend upon his training and experience as well as his interests and initiative.

Separate didactic exercises are designed to complement Clinical and Research Associateships, but Associates in all categories are welcome to attend any of the exercises which can accommodate them if their schedules permit. In addition, postgraduate instruction is available through evening courses offered by the Graduate Program of the Foundation for Advanced Education in the Sciences, Inc. (see Part Four). Associates in many program areas are expected to take advantage of academic opportunities on the NIH campus.

A candidate may enter the Associate Program as a member of the Public Health Service Commissioned Corps, or as a civilian employee.

All applicants are carefully considered. To strengthen and expand its

potential for continuing effective research, the National Institutes of Health welcomes applications from interested women and members of all minority groups.

The Clinical Associate

The Clinical Associate participates in both clinical and laboratory research. Institute programs differ in the proportion of time devoted to laboratory and clinical responsibilities.

Ward activities are under immediate supervision of competent clinical investigators, and include a wide variety of rounds, conferences, and other instructive exercises. Proximity to the patient's bedside of collaborating scientists from many biological disciplines has created an unusual opportunity for clinical investigation at the NIH Clinical Center. The environment of the Clinical Center is also enriched by the presence of medical students from country-wide medical schools with whom the Clinical Associate has close association and shares patient care responsibilities.

Clinical Associates are not in formal residency training programs, even though they may be performing many of the same functions that residents do in other hospitals. Some Associates appointed to Dermatology, Neurology, and Psychiatry programs are recommended for a limited amount of residency credit by their respective program chiefs. Associates in positions that provide further training in Internal Medicine also may receive credit upon application to the American Board of Internal Medicine.

The Dental Clinical Associate

Like his physician Clinical Associate counterpart, the Dental Clinical Associate may participate in laboratory and clinical research, while at the same time enhancing his professional skills by providing treatment to the NIH research patient pool serviced by the Dental Clinic of the National Institute of Dental Research.

During the 2-year tenure of the Associateship, full opportunity is provided for: (1) familiarization with all ongoing research programs of relevance to dentistry; (2) affiliation, in a preceptor-preceptee relationship, with one or more program leaders, so as to allow meaningful participation in a mutually acceptable area of investigation; and (3) extension of scientific background through rounds, conferences, seminars and formalized course work.

The Research Associate

The Research Associate devotes the larger portion of his time to laboratory research in the biomedical sciences. His preceptor is responsible for training him in research methodology and design, and for guiding him in the conduct of specific research undertakings and in the interpretation of results. A real effort is made to select research problems which will enable the Associate to gain breadth and perspective, encounter a variety of laboratory problems, and learn many different approaches rather than become a specialist in one or two refined techniques.

In addition, the Research Associate participates in a series of formal tutorial seminars and informal discussion groups designed in content and emphasis for prospective independent investigators. This program is designed to furnish the training in basic medical sciences normally received by Ph. D. candidates but not generally by candidates for the M.D. degree.

The Pharmacology Research Associate

Through an expansion of the NIH Associate Program, the National Institutes of Health has increased its commitment to develop scientific manpower for research in pharmacology and closely related areas of biomedical science.

Sponsored by the National Institute of General Medical Sciences in 1965, the category of Pharmacology Research Associate was established extending eligibility to basic scientists with a Ph. D. degree, in addition to those holding professional degrees such as an M.D., Phar. D., D.D.S., or D.V.M.

Pharmacology Research Associates devote the larger portion of their time to laboratory research. They receive intensive research training in a number of disciplines related to modern pharmacology. They also attend formal seminars and informal discussion groups which provide an opportunity to master selected topics perhaps not adequately covered during academic training.

The program is intended for those who have made some commitment in pharmacology or toxicology, by training or research, and for those who indicate a desire for or who need specialized experience in this field of investigation.

The Staff Associate

The Staff Associate position provides opportunities for those highly qualified candidates who could contribute significantly to research in areas which are not specifically designated in the Research or Clinical Associate categories. The Staff Associate may participate in either laboratory or clinicial research or both, depending upon the activities of the senior investigator with whom he works. Research experience may be supplemented by formal evening study courses, as well as by attendance at lectures by guest speakers and a variety of regularly scheduled seminars.

PART TWO

Applying for an Associateship

Approximately 100 Clinical Associates and 50 Research and Staff Associates are appointed annually. Associates may be employed through the Commissioned Corps of the Public Health Service or through a Civil Service mechanism. Of course, if applying through the Civil Service mechanism, it is not necessary to submit the Public Health Service forms.

Applicants usually apply during their third or fourth year of medical school for entrance on duty two years later. However, some Associate positions are appropriate for persons currently in their intern or residency training. The applicant should designate on his application the year or years he wishes his associateship to begin. Appointments will be made for 1975 and 1976, and a few will be available for 1974.

To be considered for a Clinical, Research, or Staff Associate appointment, the following forms must be received no later than April 5, 1974, in the Office of the Chief, Clinical and Professional Services, National Institutes of Health, Bethesda, Md. 20014:

- Information Record for Clinical, Research, and Staff Associate positions;
- Program Area Selection Check List;
- NIH Associate Information and Status Record;
- Interview Information Record;
- Application for Appointment as a Commissioned Officer in the U.S. Public Health Service (2 copies);
- Fingerprint chart (fingerprints may be obtained at PHS facilities or through the local police or post office);
- Data for Nonsensitive or Noncritical-Sensitive Position.

The applicant is responsible for requesting the following materials, which must be received by April 5 to complete the application:

- Three sets of references from professional persons whom the candidate has listed on the NIH information sheet (each set consists of: (1) Request for confidential evaluation of applicant for appointment as an NIH Associate; and (2) Reference Request (Commissioned Corps)).

- Two copies of all college and medical or dental school transcripts (showing class standing, if available).

A candidate's application for a commission in the Public Health Service does not commit him to accept a commission in the event he is not selected for an Associate position at NIH. However, there are many alternative opportunities for physicians and dentists in the Public Health Service which may appeal to such a candidate, and this commission application would be usable for such appointments.

Public Health Service Commissioned Corps

A uniformed service—similar to the Army, Navy, and Air Force—the Commissioned Corps is comprised largely of professionals in medical and health related fields. Uniquely, an "all officer" Corps, it serves as a mobile force to combat disease and hazards to human health.

To be eligible for the Commissioned Corps for participation as an NIH Associate, a candidate must meet the following requirements:

1. Be a United States citizen.
2. Meet the medical fitness standards.
3. Be a graduate of an accredited medical or dental school.*
4. Satisfactorily complete an internship approved by the Council on Medical Education of the American Medical Association. (However, application will be accepted when internship is an integral part of medical school curriculum or incorporated as part of residency training.)

An appointment in the Commissioned Corps offers unusual opportunities for professional development. It provides a climate of scientific inquiry and application with contemporaries from a variety of other health related disciplines. Pay and allowances are comparable to those of officers of the Armed Forces. In addition, the PHS provides medical care for officers and dependents; tax-free quarters and subsistence allowance; commissary, post exchange, and officers' club privileges; and 30 days annual leave.

*An exception to this would be Ph. D. candidates for the PRAT Program.

Early Commissioning Program for Medical Students (PHS Senior COSTEP Program)

Qualified candidates who will be in their senior or last year of medical school during academic year 1974–75 may apply for an Associateship through this program. Candidate may apply for duty to begin either (A) following one or more years of residency training or (B) immediately after internship.

Successful candidates are appointed and placed on active duty as commissioned officers in the Reserve Corps of the Public Health Service during their senior or final year. They receive full pay and allowances as Junior Assistant Health Service Officers (equivalent to Navy Ensign), plus payment of tutition, fees, and other related expenses. In return for this financial support, they are obligated to serve on active duty as medical officers with the PHS for a minimum of 2 years.

To be eligible for early commissioning, the student must meet the following requirements of the PHS:

1. Be a citizen of the United States.
2. Meet the medical fitness standards.
3. Be enrolled in good standing in an accredited school of medicine (or osteopathy) in the senior or final year, and have begun formal studies required as part of the curriculum for the senior or final year of medical school on the date of entry on active duty.
4. Agree in writing to serve a minimum of 2 years with the sponsoring PHS program.

Candidates selected may serve their Internships either within or outside the Public Health Service. Students electing and matched through the National Intern Residency Matching Program with Internship with PHS hospitals will be continued on active duty with the pay and allowances of their rank. (Note: this time does not count toward the obligated service.) Students matched for Internships with other hospitals will be placed in an inactive duty status and will receive their pay or stipend from the training hospital. Following Internship candidates will usually complete residency training (usually one year for NIH programs). Some appointments will be made for immediate active duty following Internship.

NIH is seeking women candidates with an interest in research. They may enter associateships either as a PHS Commissioned Officer or in a civilian capacity. However, to receive the benefits of the Early Commissioning (Senior COSTEP) Program, *all* candidates must qualify for and serve as Commissioned Officers in the Public Health Service.

Applications cannot be considered from members of another uniformed service or anyone having a service commitment upon graduation other than to the Public Health Service.

Method of Selection—Matching Program

Selections for the Clinical, Research, and Staff Associate appointments are made through a matching process in which the candidate's preferences are matched with the Institute preferences.

In the application packet, a candidate will find several sheets, each headed "Program Area Selection Check List." After reading Part Three of this catalog, he should check off on these sheets the areas in which he is interested. He does not indicate his preferences at this point, and he is not limited to any particular number of choices. The check marks that he makes will determine the laboratories and branches to which his application will be circulated at the National Institutes of Health.

After thorough review of all applications by the Institutes, a limited number of candidates will be selected for personal interviews to be held during a 2-week period from June 10 through 21. Candidates should be prepared to come to NIH for an interview on short notice on any date within this period, at their own expense. All interviews are by invitation and are held only during this scheduled period.

The Clinical and Professional Services Section will set up the interviews and advise candidates when to report. Candidates are requested not to attempt to arrange their own interviews.

PART THREE

Program Areas for Which Candidates May Apply

EACH of the major NIH components has prepared a description of its program areas for which Associates may seek appointment. Due to diversity of the operations and programs within these major components, the descriptions do not follow a pattern. In effect, however, all of these descriptions are meant to anticipate the questions which applicants may have in selecting the program areas for which they wish to be considered. It should me noted that a candidate is not limited as to the number or kinds of positions for which he may apply.

National Cancer Institute

Director, Frank J. Rauscher, Jr., Ph. D.
Clinical Director, Alfred S. Ketcham, M.D.

Laboratories and Branches

Director, Division of Cancer Biology and Diagnosis, Nathaniel I. Berlin, M.D., Ph. D.

Associate Director for Program Planning, Irvin C. Plough, M.D.

Chief, Laboratory of Biochemistry, Robert F. Goldberger, M.D.

Chief, Laboratory of Biology, Walter E. Heston, Ph. D.

Chief, Labroatory of Cell Biology, Lloyd W. Law, Ph. D.

Chief, Laboratory of Molecular Biology, Ira H. Pastan, M.D.

Chief, Laboratory of Pathology, Louis B. Thomas, M.D.

Chief, Laboratory of Pathophysiology, Pietro M. Gullino, M.D.

Acting Chief, Laboratory of Physiology, Nathaniel I. Berlin, M.D., Ph. D.

Acting Chief, Laboratory of Theoretical Biology, Mones Berman, Ph. D.

Chief, Dermatology Branch, Marvin A. Lutzner, M.D.
Chief, Breast Cancer Program Coordinating Branch, Erwin P. Vollmer, Ph. D.
Chief, Immunology Branch, William D. Terry, M.D.
Chief, Metabolism Branch, Thomas A. Waldmann, M.D.
Chief, Radiation Branch, Ralph E. Johnson, M.D.
Chief, Surgery Branch, Alfred S. Ketcham, M.D.

Director, Division of Cancer Cause and Prevention, James A. Peters, D.V.M.
Associate Director for Program, Gio B. Gori, Ph. D.
Associate Director for Viral Oncology, John B. Moloney, Ph. D.
Chief, Viral Biology Branch, Robert A. Manaker, Ph. D.
Chief, Viral Carcinogenesis Branch, Robert J. Huebner, M.D.
Chief, Viral Leukemia and Lymphoma Branch, George J. Todaro, M.D.
Associate Director for Carcinogenesis, Umberto Saffiotti, M.D.
Chief, Biology Branch, Herbert J. Rapp, Sc. D.
Chief, Chemistry Branch, Harry V. Gelboin, Ph. D.
Acting Chief, Experimental Pathology Branch, Jerry M. Rice, Ph. D.
Chief, Carcinogen Metabolism and Toxicology Branch, Elizabeth K. Weisburger, Ph. D.
Chief, Carcinogen Bioassay and Program Resources Branch, Norbert P. Page, D.V.M.
Chief, Lung Cancer Branch, Michael B. Sporn, M.D.
Associate Director for Field Studies and Statistics, Marvin A. Schneiderman, Ph. D.
Chief, Biometry Branch, William A. Haenszel, M.A.
Chief, Epidemiology Branch, Robert W. Miller, M.D., Dr.P.H.

Director, Division of Cancer Treatment, C. Gordon Zubrod, M.D.
Deputy Director, Seymour Perry, M.D.
Associate Director for Cancer Therapy Evaluation, Stephen K. Carter, M.D.
Associate Director for Medical Oncology, Paul P. Carbone, M.D.
Chief, Medicine Branch, Vincent T. DeVita, M.D.
Chief, Pediatric Oncology Branch, John L. Ziegler, M.D.
Chief, NCI-VA Medical Oncology Branch, Oleg S. Selawry, M.D.
Associate Director for Experimental Therapeutics, Vincent T. Oliverio, Ph. D.
Acting Chief, Laboratory of Chemical Pharmacology, Richard H. Adamson, Ph. D.
Chief, Laboratory of Molecular Pharmacology, Kurt W. Kohn, M.D., Ph. D.
Chief, Laboratory of Toxicology, Anthony D. Guarino, Ph. D.

Chief, Laboratory of Tumor Cell Biology, Robert C. Gallo, M.D.

Associate Director for Drug Research and Development, Saul A. Schepartz, Ph. D.

Chief, Laboratory Research, Abraham Goldin, Ph. D.

Acting Chief, Laboratory of Experimental Chemotherapy, Abraham Goldin, Ph. D.

Chief, Drug Development Branch, Harry B. Wood, Jr., Ph. D.

Chief, Drug Evaluation Branch, John M. Venditti, Ph. D.

Associate Director for Baltimore Cancer Research Center, Michael D. Walker, M.D.

Chief, Clinical Branch, Michael D. Walker, M.D.

Acting Chief, Laboratory of Pharmacology, Carl C. Levy, Ph. D.

Division of Cancer Biology and Diagnosis

A broad range of research is carried out in both basic laboratories and clinical branches under the general direction of Dr. Nathaniel I. Berlin.

The Laboratory of Biochemistry consists of six sections. The Section of Cellular Regulation is concerned with the mechanism of regulation of gene expression in bacterial cells, with special emphasis on enzyme induction and repression. Work in this area is carried out at the cellular level, utilizing physiological and genetic techniques, and with coupled systems for the synthesis of specific messenger-RNA and enzymes *in vito*. In addition, this section conducts studies on the mechanism of regulation of gene expression in mammalian cells, as well as the mechanism of action of human interferon.

The Section of Nucleic Acid Enzymology is concerned with detection and study of enzymes involved in nucleic acid synthesis and degradation. Systems under study include DNA enzymes related to simian virus 40 replication; bacterial restriction endonuclease and corresponding methylase; and bacterial polynucleotide phosphorylase. Emphasis is placed on reaction mechanisms by two main approaches: (1) nature of substrates and products; and (2) relation of enzyme structure to function. A variety of modern techniques of nucleic acid and protein chemistry are employed.

The Section of Biochemistry of Gene Regulation studies control of gene expression in eukaryotic cells and its application to clinical medicine. The effects of steroid hormones on enzyme induction both in cultured cells and cell hybrids are investigated, along with studies on steroid receptors in human leukemia and breast cancer. Techniques of cell culture, cell fusion, chromosome banding, protein synthesis, and affinity chromatography are among those utilized.

The Section of Biosynthesis conducts research on the synthesis, assembly, and functional properties of cellular membrane systems. Cur-

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rent studies deal with regulation of collagen biosynthesis, the properties of membrane-associated DNA polymerases, alterations in synthesis of membrane "structural" proteins in transformed cells, and electron microscopy of surfaces of cells interacting in the immune response.

The Section of Cell Physiology and Oncogenesis investigates cellular and molecular events in the neoplastic transformation of mammalian cells in culture. The goals of this section include early detection of neoplastic transformation and elucidation of the cause and effect relationships in oncogenesis. Among the tools employed are long-term tissue culture, modern biochemical methods, animal transplantation, microscopy-photography, and radio-isotopic techniques.

The Section of Protein Chemistry is investigating biochemical changes accompanying the maturation of granulocytes in bone marrow, interactions between cells involved in the immune response, and the transfer of genetic information through the cellular uptake of isolated chromosomes.

In the Laboratory of Biology, carcinogenesis is studied in the broad biological sense. Attention is given to the manner in which genetic, viral, hormonal, and immunological factors as well as chemical and physical carcinogens lead to the occurrence of cancer. Special emphasis is given to the mammary tumor system in mice—the morphologic and biochemical nature of the virus particle, the identification of various lines of the virus and its transmission, particularly its genetic transmission. Genetic, immunologic, and chemical procedures are combined with electron microscopy. This work is supported with other basic studies in cytology and biochemical genetics in the mouse.

Personnel of the Laboratory of Cell Biology have diverse interests focusing upon the study of transformation of a normal cell to a neoplastic cell. Techniques from the fields of virology, immunology, immunochemistry, biochemistry, biophysics, tissue culture, somatic-cell hybridization and electron microscopy are used. Some of the specific problems pursued are: genetic control of the synthesis of abnormal proteins produced by malignant cells (principally plasma cells), role of cell membranes in regulating differentiation and growth, identification and study of tumor antigens and of the specific immune reactions initiated, solubilization and purification of transplantation and tumor antigens, influence of somatic cell hybridization on expression of genetically determined events and ultrastructural analysis and molecular biology of viral oncogenesis.

The Laboratory of Molecular Biology investigates gene function in animal and bacterial cells. Studies are devoted to identifying factors which control and alter gene expression. One of these is cyclic AMP. Transcription is studied in purified cell-free systems, mutants defective in transcription are isolated and employed to detect these regulatory compounds. Other studies are directed towards investigating the molecular basis of genetic recombination. These studies employ the bacteri-

ophage λ and its host, *E. coli*. Mutants defective in recombination are isolated and the nature of their defects analyzed by both genetic and biochemical methods.

New knowledge of how control systems operate in bacteria are applied to studies on cultured animal cells. Current efforts are directed to understanding the role of cyclic AMP in cellular transformation.

The Laboratory of Pathology of the National Cancer Institute offers a 2-to-4-year training program for residents in pathologic anatomy in the Clinical Center, National Institutes of Health, Bethesda, Maryland. The program which is fully approved for Board certification provides well supervised instruction and experience in the performance of autopsies, surgical pathology and exfoliative cytology. Special training in the subspecialties of cardiac pathology, hematopathology and neuropathology can be arranged. Opportunity is provided for learning many research techniques, particularly electron microscopy, fluorescence microscopy, tissue culture, histochemistry, autoradiography and cytogenetics. Individual or collaborative participation in clinical or laboratory research projects by the residents and selected Research Fellows and Visiting Scientists is encouraged.

In addition to the autopsy, surgical pathology and cytodiagnostic services, the laboratory also carries on a broad research program in experimental pathology. Research projects include studies of oncogenic viruses and viral carcinogenesis, chemical carcinogenesis, immunopathology and tumor immunology, experimental embryology as related to cancer, and biochemical and ultrastructural studies of viruses and neoplastic cells.

In the Laboratory of Pathophysiology research is directed towards an understanding of the conditions necessary to arrest neoplastic growth and/or induce regression of a neoplastic cell population. One group of projects involves studies on mammary tumor regression. Investigations underway include: the role of RNA synthesis; growth arrest produced by cyclic AMP, cycloheximide and actinomycin D; host-angiogenesis related to growth potential of neoplastic and preneoplastic tissues; and cell loss through the circulation as a contributing factor to tumor regression. Another group of projects deals with the initiation of DNA synthesis in mammalian cells, in particular, the role of poly ADP-ribose in triggering DNA replication and the consequences of inhibiting poly ADP-ribose synthesis. Studies on cell to cell interaction utilize an artificial capillary network which is able to sustain growth and permit the formation of solid tumor masses *in vitro*.

In the Laboratory of Physiology there are a number of projects which bear on the physiological and biochemical properties of the growing tumor and its impact on the host. Approaches are made by studies on: the mechanisms of synthesis and secretion of hormones in the thyroid gland and thyroid tumors, and the nature of the growth of the thyroid

gland in response to stimuli; urinary excretion of purine and pyrimidine congeners and their relation to various types of leukemia; partition of the total energy expenditure of the tumor-bearing host between the host and the tumor. There are also a number of projects involving fundamental studies of the effects of radiation on proteins and on living organisms. These include studies of: effect of ionizing radiation on enzyme systems entailing the partial and complete destruction of active centers; antibody formation following multiple irradiation and immunization procedures; radiation damage and recovery of the hematopoietic system; and tissue transplantation and the immune response.

The Laboratory of Theoretical Biology is concerned with the development of theories and mathematical and computational techniques for formal, quantitative studies of the structure, function and dynamics of biological systems. Of particular interest is the development of formal models for the kinetics of metabolites related to endocrine systems. Studies of membrane structure and transport are also conducted. Although the group is predominantly theoretical, experimental work related to problems being investigated is carried out within the laboratory and in collaboration with experimental groups.

In the Dermatology Branch, studies are designed to identify and characterize the biologic behavior patterns of epithelial and lymphoid tissues in normal and pathologic circumstances, using primarily the techniques of biochemistry, electron microscopy, and tissue culture. The chemistry, structure, and function of keratin, melanins and epidermal cell organelles are being investigated, with particular reference to the genodermatoses of man and animals.

In the Immunology Branch, the mechanisms of normal and disordered immune response are under investigation. Immunochemical, biochemical, physical, tissue culture, and isotope incorporation techniques are used in research on the structure, biosynthesis, and genetic control of antibodies and of immune cell function. Cell surface antigens and receptors (histocompatibility, tumor specific, differentiation, and others), immune cell recognition systems, and multiple aspects of cellular immunity are parts of fundamental and clinical studies in tumor immunology, tumor immunotherapy, immunodiagnosis of cancer, and transplantation.

The Metabolism Branch is studying the metabolic and immunologic antecedents and consequences of cancer. Investigations are directed toward a broad range of immunological problems, especially as they involve immunodeficiency states in man associated with a high incidence of malignancies. The studies are concerned with the mechanisms of abnormalities of circulating and cellular immune responses in patients with such disorders as agammaglobulinemia, the Wiskott-Aldrich syndrome, ataxia telangiectasia, intestinal lymphangiectasia and inflammatory bowel disease. Special attention is given to the study of cell coopera-

tion in the immune response, factors controlling differentiation of cells, on membrane associated receptors of lymphoid cells, on mechanisms of lymphocyte mediated cytotoxicity, on the role of macrophages in the immune response and on factors controlling immunoglobulin metabolism.

The research program also includes studies of porphyrin metabolism, calcium metabolism, serum protein metabolism, the hormonal control of growth, membrane transport and proline biosynthetic pathways.

The Radiation Branch is responsible for the development of new techniques in the treatment of cancer using irradiation alone and in combination with other modalities, especially chemotherapy. Clinical investigations receiving major emphasis are the malignant lymphomas and chronic leukemia, bone neoplasms, and cancer of the upper air passages and lungs. Active clinical studies are underway in the areas of tumor immunology and radiochemical modification of radiation response. Research in the Radiation Physics Section is closely integrated with clinical radiotherapy and includes computer applications to medicine. Laboratory research is designed to explore the feasibility of new therapeutic approaches and includes radiobiological studies with 14 MeV fast neutrons.

The Surgery Branch investigates immunologic, physiologic, metabolic, hormonal and nutritional factors that influence the results of surgery for malignant disease. The studies are conducted in patients with cancer of the breast, head and neck region, female pelvic organs, genitourinary system, and melanoma and sarcoma. All surgical treatment protocols utilize appropriate adjunctive therapy combinations of immunotherapy, chemotherapy and radiotherapy.

Division of Cancer Cause and Prevention

In the Division of Cancer Cause and Prevention, a major responsibility of scientists under the direction of Dr. James A. Peters is planning and implementing programmed research on cancer causation, patterns of cancer occurrence, and means for cancer prevention.

A program of virus-cancer studies is carried out in the Viral Biology, Viral Leukemia and Lymphoma, and Viral Carcinogenesis Branches under the Office of the Associate Director for Viral Oncology. Research activities with DNA and RNA viruses in biological systems range from the subcellular level to that of the intact host, including man. A special program is expanding basic and applied research on the possible viral etiology of leukemia. Institute scientists are collaborating with non-Federal investigators in multidisciplinary studies on animal tumor viruses and in the search for viruses in human cancer.

A special program to provide resource needs of cancer virologists, such as standardized cell lines and new varieties of research animals, is also located in the Viral Carcinogenesis Branch.

Chemical hazards in man's environment are of special concern to

investigators in the Chemistry, Biology, Experimental Pathology, Carcinogen Metabolism and Toxicology, Carcinogen Bioassay and Program Resources, and Lung Cancer Branches under the Office of the Associate Director for Carcinogenesis. Emphasis here is placed on the interaction of host factors with multiple environmental factors.

The Epidemiology Branch plans and conducts studies using data from existing sources such as vital and employment records and clinical observations. These investigations seek clues to cancer causation through analysis of interrelationships in the human and domestic animal populations with respect to their total environment and inheritance.

Some of the biostatistical studies carried out by the Biometry Branch are also concerned with the causes of cancer. Others are devoted to evaluating methods for diagnosing and treating cancer. In this connection, more than 100 hospitals in the United States are cooperating in a patient registration and followup program.

Division of Cancer Treatment

An intensive program of laboratory research and clinical investigation concerned with the therapy of cancer is under the direction of Dr. C. Gordon Zubrod. Although emphasis is placed on anti-tumor drug development and the chemical control of cancer, the division also emphasizes treatment utilizing not only combinations of drugs but combinations of drugs with other modalities of therapy including surgery, radiation, and immunotherapy.

Cancer Therapy Evaluation is involved in the planning and directing of the Clinical Contract Program, testing combined modality therapy approaches and the clinical evaluation of new investigational cancer chemotherapy agents. Direction is also given to the evaluation of the effectiveness of specific types and methods of cancer therapy.

The Combined Modality Branch implements and monitors a comprehensive cancer therapy Clinical Contract Program designed to provide specific and immediate clinical trials of combined modality approaches to the therapy of specific tumors. It is responsible for bringing together, under contract, expertise in chemotherapy, surgery, radiotherapy, and immunotherapy in the design of comprehensive therapeutic programs geared to the eventual cure of specific disease entities. It is responsible for maintaining continuing liaison with various advisory and consultant groups established as working committees to study the effectiveness of specific types and methods of cancer therapy.

The Investigational Drug Branch implements and monitors a comprehensive cancer therapy Clinical Contract Program designed to provide highly specific and immediate clinical trials of anticancer drugs that have demonstrated high activity in animals in the preclinical phase of the drug development aspect of the Cancer Therapy Program. The

Branch is responsible for the communication and filing of all information required by the Food and Drug Administration in connection with the Drug Development Program of the National Cancer Institute.

The Medical Oncology Area emphasizes a multifaceted approach to improve the clinical control of patients with leukemia, lymphoma, and solid tumors with major efforts in combination chemotherapy, pharmacology, cell kinetics, cytogenetics, biochemical characteristics of normal and malignant cells and immune mechanisms. Clinical Associates are assigned to the wards during their first year. This year serves as qualification of one residency year for board requirements in Medical Oncology. The optimal use of new agents, combination of drugs, maximal supportive care with platelet and leukocyte transfusions, and patient protection techniques are investigated in a broad scale clinical program aimed at improving survival and eradicating the total tumor cell populations in these patients. During the second year, laboratory experience under the guidance of senior investigators is offered.

The Medical Oncology Area consists of the Medicine Branch, the Pediatric Oncology Branch, the NCI–VA Medical Oncology Branch, and the Medical Breast Cancer Service.

The Medicine Branch is a unit whose clinical programs emphasize the diagnosis, staging and treatment of the malignant lymphomas, and investigation and management of ovarian carcinoma, endocrine secreting tumors, melanoma, cancer of the pancreas, and the myeloproliferative disorders. Training in clinical diagnostic procedures related to cancer such as bone marrow examination, liver biopsy, and peritoneoscopy is emphasized. An active consultation service works closely with other units at the NIH including the Surgery Branch and Radiation Branch.

The research program focuses on the general area of kinetics of neoplastic and hemopoietic cells and the biochemical pharmacology of antineoplastic agents.

The NCI–VA Medical Oncology Branch is located in the Veterans Administration Hospital, Washington, D.C. The branch consists of 28 ward beds and two laminar air flow rooms. Patient accrual is from the various medical and surgical services at the VA Hospital and by outside referral. The principal aims of the branch are to develop more effective therapy for patients with bronchogenic carcinoma, and to study the clinical pharmacology of promising new chemotherapeutic agents coming into clinical trial for the purpose of determing optimal doses and schedules of treatment and to determmine the type and range of toxicity associated with given drugs (Phase I).

The development of more effective therapy of bronchogenic carcinoma is pursued on several levels. The biological behavior of the various cell types of bronchogenic carcinoma is studied by analysis of cell kinetics both at the primary site and at various metastatic sites, by following the production of various marker substances including hormone and embryonic

antigens both *in vivo* and *in vitro*, and by studying factors that play a role in drug uptake by tumor cells including the status of microvasculature of the tumor and the effects of various vasoactive drugs on influencing vascular permeability and drug intake.

The Pediatric Oncology Branch presently deals with three major areas of investigation of the acute leukemias: (1) chemoimmunotherapy, (2) transfusion support and bone marrow transplantation, and (3) diagnostic and preventive techniques applicable to the infectious complications of the compromised host. The program emphasizes the clinical management of the patient with leukemia, and the teaching program is currently oriented in the areas of hematology, infectious diseases, and chemotherapy. The interaction of clinical problems and their investigation either in the laboratory or by clinical trial are emphasized.

Specific therapeutic programs in the acute leukemias are designed to effect maximal reduction of the malignant cell populations the goal of which is significant prolongation of remission. Comprehensive immunologic assays of patients are performed in order to assess the utility of various *in vitro* and *in vivo* techniques in understanding the natural history of these diseases and the influence of treatment. These techniques include skin testing, mixed leukocyte cultures, and blastogenic responses to various antigens and mitogens. Several basic studies of tumor immunology and cellular pharmacology are underway.

Transfusion and support studies explore the physiologic replacement of granulocytes and platelets in patients with compromised bone marrow function. Assays of platelet and granulocyte compatibility and function are undertaken, and animal experiments are designed to improve the procurement, storage, and transfusion of these blood components. A major area of interest is hematologic reconstitution through bone marrow transplantation. Studies in this area include an analysis of factors leading to engraftment, prevention and modification of graft-versus-host syndrome, and various assays of bone marrow physiology.

In the infectious disease program, diagnostic and preventive maneuvers are designed to reduce the significant morbidity and mortality of infectious complications in the compromised host. These maneuvers include the use of laminar air flow isolation and prophylactic antimicrobial agents in a controlled setting. Major studies on microdetermination of circulating endotoxin and on the molecular identification of latent viral genetic material illustrate newer diagnostic approaches to infectious disease. Developmental trials of antibacterial vaccines and antiviral compounds are also given emphasis.

The Medical Breast Cancer Service is concerned with all aspects of patient care beginning with the diagnosis of carcinoma of the breast. Emphasis is given to the utilization of long-term adjuvant chemotherapy following primary mastectomy and, to the use of adjuvant chemotherapy combined with hormone therapy for those patients demonstrating their

first recurrence of disease. Additional programs involve the evaluation of new chemotherapeutic regimens and approaches in patients with metastatic disease. These latter regimens are evaluated with a view toward utilizing them in an adjuvant setting in the future. Ancillary clinical studies are concerned with tumor cell markers, radioisotope scanning approaches, radiotherapeutic problems, pharmacologic evaluations, hormone assay determinations, and immunologic investigations.

The Experimental Therapeutics Area studies many facets of the interactions between drugs and living materials. It includes biochemical pharmacology, toxicology, physiological disposition, drug metabolism, molecular biology, mechanism of action, and comparative pharmacology. In addition, it works closely with the Medical Oncology Area with regard to clinical research problems. In the Office of the Associate Director for Experimental Therapeutics, studies on the transport of material between blood and brain, blood and cerebrospinal fluid, and cerebrospinal fluid and brain are conducted as well as investigations aimed at improving the chemotherapeutic treatment of central nervous system and meningeal tumors.

The Office of the Associate Director, in addition to an overall administrative responsibility for four laboratories, conducts a research effort in the area of the exchange of various physiological and pharmacological substances between blood, cerebrospinal fluid, and brain extracellular and intracellular fluids. Both experimental and computer studies are designed and executed in attempt to increase our understanding of the basic transport mechanisms involved in the system and to examine the delivery of drugs to normal tissue and tumor sites within the brain, spinal cord, and meninges. These efforts are intended to elucidate new and better routes of drug administration, find key physicochemical and structural properties of potential chemotherapeutic agents which will optimize tissue delivery, and develop ways to transiently modify the "transport barriers" and subsequently increase drug uptake. Another important area of research concerns biochemical pharmacology of antitumor drugs in preclinical systems, an effort which blends well with ongoing activities in the laboratory within the Experimental Therapeutics Area.

The Laboratory of Toxicology functions to investigate and describe the qualitative and quantitative toxicity of potential antineoplastic drugs using animal test systems. Young and old animals of both sexes, as well as pregnant animals are included in these studies. Treatments range from acute to chronic. Adverse effects of oncolytic agents in man are correlated with those observed in lower species in an effort to increase the predictability of the animal test systems. Attempts are made to define the predictability, reversibility, and mechanisms of drug-induced toxicity. The pathogenesis of the lesions detected is studied at every level from the morphologic to the molecular. Wherever possible, antidotes are sought. In order to achieve the greatest therapeutic effect at the least cost in

serious side effects, a variety of experimental treatment regimens are tested. The Laboratory of Toxicology also investigates whether proposed drug combinations alter toxicity and therapeutic efficacy by evoking changes in drug binding, absorption, distribution, and/or metabolism. The laboratory is composed of three scientific units: Biochemistry, Comparative Pathology and Drug Interactions. All the functions of the laboratory are closely integrated with the development of new anticancer agents and ongoing clinical studies.

The Laboratory of Molecular Pharmacology is engaged in fundamental studies on the mechanisms of drug action on mammalian cells, particularly actions involving nucleic acids and related structures. Of major interest are (1) interactions between drugs and macromolecules studied by physical chemical techniques, (2) effects on the synthesis and function of nucleic acids and related structures in cells, and (3) relations between molecular effects of drugs and their biological effects on cells. The drugs studied are actual or potential chemotherapeutic agents or compounds having special properties that facilitate relevant studies of intracellular processes.

The Laboratory of Chemical Pharmacology is primarily engaged in studies of the pharmacology of new and established antitumor agents and other drugs used in patients with cancer. Clinical Associates assigned to this area spend their first year as primary physicians on the wards of the Medical Oncology Area. During the second year, they participate in laboratory research projects under the direction of a Senior Investigator in the Laboratory of Chemical Pharmacology. A wide range of research topics related to the pharmacology of antineoplastic agents are under active investigation. Particular emphasis is placed on the pharmacokinetics and cellular transport of the agents, the effects of the agents on the cell cycle, the disposition of antitumor agents in animals and man and the enzyme systems involved in the metabolism of the antitumor agents. Other studies include mechanisms of resistance to anticancer agents; structure activity relationships of antitumor agents; new approaches to cancer chemotherapy; the untoward effects of drugs resulting from inherent physical-chemical properties and/or interactions with other concomittantly used drugs; and biological markers which will aid in the diagnosis and treatment of the precancerous state as well as frank neoplasia. Agents of recent interest have been guanazole, gallium, alanosine, nitrosoureas, rifampicin analogs, interferon and interferon-inducers, carboxypeptidase G_1, DNA and RNA binding antibiotics, hycanthone, and the folic acid antagonists. Biological markers of recent interest have been alpha-fetoprotein, carcinoembryonic antigen, methylated nucleic acid bases, HCG and polyamines. In all areas of interest, both fundamental and pragmatic approaches are utilized.

The Laboratory of Tumor Cell Biology has several major research interests including studies on: (1) the controls of cellular growth,

differentiation, maturation, and the process of malignant transformation in human cells; (2) mechanism of action of new antitumor agents and elucidating alterations involved in the development of resistance to drugs; (3) development of molecular probes for the presence of small numbers of neoplastic cells; (4) cytogenetic techniques are an integral part of both cell kinetic and biochemical studies; (5) purification and biochemical and biological characterization of DNA polymerases from human cells and from oncogenic RNA viruses ("reverse transcriptase" or RNA-dependent DNA polymerase) have become a major aspect of the entire program. These studies are designed to aid in the understanding of the function of these enzymes, *e.g.,* appearance in the cell cycle, activity with certain compounds, role in cellular differentiation, and role in neoplastic transformation. The questions of whether any of the enzymes in cells are viral in origin and whether DNA and RNA polymerases of neoplastic cells differ qualitatively or quantitatively from those of normal cells are under intense study; (6) development of new molecular probes for virus specified information in cells; (7) new antiviral agents are evaluated in a number of biological and biochemical systems; and (8) the role of transfer RNA in differentiation and neoplastic transformation is also under investigation. Overall the major goals may be summarized as attempts to develop new approaches for diagnosis, prognosis, and therapy of human neoplasia based on information derived from basic studies on neoplastic cells and on the conversion *in vitro* of normal cells to neoplastic cells.

Drug Research and Development is engaged in a multidisciplinary approach to the fundamental and developmental aspects of cancer chemotherapy. Through contracts and direct laboratory operations it carries out programs directed toward the development of new and better antitumor agents.

In the Office of the Associate Director selected research programs are concerned with fundamental chemotherapeutic, biological, biochemical and immunological investigations of the mechanism of action of antitumor and antiviral agents, new therapeutic models, metastasis, drug resistance, animal genetics and disease control.

The Laboratory of Experimental Chemotherapy undertakes fundamental studies of the biology of normal and tumor cells in chemotherapy; investigation of metabolic control mechanisms in development, differentiation, rapid growth and steady-state maintenance; alteration of regulatory mechanisms in malignant cells; study of basic cellular phenomena and the synthesis of new inhibitory agents to interfere with these processes; investigation of host immunological factors in tumor growth and their interaction and studies of the combined effects of immunity and chemotherapy. The studies are correlated with the clinic in the development of modalities of therapy, special problems and therapeutic principles.

The Drug Development Branch is charged with the responsibility for securing both synthetic materials and natural products for evaluation as potential chemotherapeutic agents and for use in toxicological and clinical studies. There are opportunities to work on the theoretical aspects of structure-activity relationships and the management problems associated with a large program in drug development. In addition, laboratory activities are conducted in new drug synthesis, natural products isolation and structure determinations, and experimental parenteral drug formulation.

The Drug Evaluation Branch is engaged in a board approach to the recognition of potential new anticancer drugs and to fundamental and developmental aspects of antitumor chemotherapy. Activities are conducted both through contract and direct laboratory operations. Studies include: empirical testing of unknown materials for biological activities of predictive value to the clinic; detailed preclinical evaluation of drugs that emerge as potential clinical candidates; studies in molecular biology; mechanism of drug action and other biochemical aspects of cancer chemotherapy; mechanism of drug resistance and means of overcoming resistance; establishment of new therapeutic principles and procedures for the management of tumor growth in animals; structure-activity relationships; combination chemotherapy; possible role of host immunity in chemotherapy; the development of model systems to study the kinetics of tumor and host cell proliferation and effects of drugs thereon.

The Baltimore Cancer Research Center conducts a collaborative integrated program of laboratory and clinical research in the therapy and management of cancer patients. The Clinical Oncology Section (Dr. Peter H. Wiernik, Head) is concerned with the medical care and treatment of patients with leukemia, lymphoma and specific solid tumors utilizing combination chemotherapy and other treatment modalities. The Neurosurgical Brain Tumor Program is concerned with the diagnosis, operative intervention and therapy of primary and secondary cancers of the central nervous system (Dr. Michael D. Walker, Head) and the Radiotherapy Section (Dr. Roger Byhardt, Acting Head) provides intensive cobalt treatment programs. A major microbiologic program in infectious complications in the treatment of malignant disease (Dr. V. M. Young, Head) includes the evaluation and use of protected patient environment employing the concept of laminar air flow. The patient care pharmacy, blood component replacement therapy program including leukocyte and platelet transfusions, clinical pharmacologic investigation of anticancer drugs and computer-oriented research programs in patient care round out the program. The clinical program is a collaborative endeavor between the Division of Hospitals (USPHS Hospitals-Baltimore) and their fully approved residency training programs in major medical specialties.

The Laboratory of Pharmacology is concerned with basic and applied research programs in the treatment and investigation of neoplastic disease. A major program in biochemical pharmacology of chemotherapeutic agents (Dr. Nicholas Bachur, Head) evaluates metabolism), physiologic distribution, disposition and mechanism of action of anticancer drugs, and collaborates with the Clinical Branch. Drug enzyme interactions and cancer marker programs (Dr. Carl Levy, Head) study cellular proliferation characteristics in relation to therapeutic modalities. Basic and applied tumor immunology programs (Dr. Michael Mardiney, Head) study the immune mechanisms of cancer.

National Eye Institute

Carl Kupfer, M.D., Director

The National Eye Institute conducts, fosters, and supports research on the cause, natural history, prevention, diagnosis, and treatment of disorders of the eye and visual system.

The Institute selects three Clinical Associates from those candidates who have completed an accredited 3-year ophthalmology program. Clinical Associates spend time in both clinical and laboratory research, including patient care activities.

One Research Associate will be selected by the National Eye Institute to be called to duty one year after graduation.

In selection of Clinical and Research Associates, preference will be given to those who will continue their research training either at the National Institutes of Health or in an academic setting elsewhere with an eventual career in full-time clinical or laboratory research.

Laboratory and Clinical Research

The National Eye Institute has developed its clinical and research program into two major branches, the Laboratory of Vision Research and the Clinical Branch. The Laboratory of Vision Research plans and conducts fundamental laboratory research on the visual system. This includes anatomy, biochemistry, physiology, embryology, pharmacology, and experimental pathology of the visual system.

The Clinical Branch plans and conducts clinical research into the causes, prevention, diagnosis, and treatment of the visual system. It translates laboratory research results into clinical application, directs and administers the Institute's clinical care program and assures functioning of the eye ward and clinic in the NIH Clinical Center.

It is the Clinical Branch's responsibility to investigate the causes and prevention of blindness. The major areas under study are cataracts of unusual origin, selected corneal diseases, glaucoma, melanotic lesions of the globe, ophthalmic genetics, and vascular diseases.

(1) Cataracts of unusual origin are being studied in clinical, biochemical, histochemical, and histopathologic correlative research projects.

(2) In corneal diseases, nonresponsive inflammatory lesions, dystrophic disorders, degenerative disorders, and metabolic disorders having corneal manifestations are included in studies of diagnostic procedures and therapeutic trials. Systemic tissue antibody studies are underway in cases of early corneal graft rejection.

(3) In glaucoma, studies are directed to the understanding of intraocular fluid dynamics in the normal and glaucomatous eye. Studies of the

parameters of intraocular pressure are of primary concern. Pharmacologic agents are being tested in connection with glaucoma, ocular hypertension, and steroid response of intraocular pressure. Innovative surgical techniques are being assessed in selected cases of severe and congenital glaucoma.

(4) Studies on methods to improve the diagnosis and therapy of melanotic lesions of the globe are underway.

(5) Ophthalmic genetic studies include clinical, biochemical, and electrophysiologic studies of hereditary retinal diagnosis problems. In the retinal degnerative disorders, there is a premature death of certain cells within the retina which is the neural and biochemical mediator of vision. While previous research efforts have been confined to areas of diagnosis, classification, and family studies, current investigations are expected to provide a better understanding of the disease itself. The night blindness syndromes, familial vascular retinopathies, familial macular disease, and color deficiency are being emphasized.

(6) In vascular diseases, diagnostic investigations are being conducted to define underlying systemic disease in conditions such as diabetic retinopathy, macular degenerations, and other retinal vascular diseases or vascular disease of the optic nerve. The effect of photocoagulation treatment and cyrothrapy is also being investigated.

The Laboratory of Vision Research is composed of the following disciplines:

(1) Biochemistry. This section is presently conducting studies on the chemistry and metabolism of the lens and cornea, with particular emphasis on the formation and prevention of sugar cataracts in experimental animals. The physical chemistry of model gel systems, structural and functional aspects of the bovine rhodopsin molecule, protein synthesis in the retina, biochemistry of visual pigments, biochemistry of the pigment epithelium, and the metabolisms of photoreceptors are also under investigation. Finally, synthesis of sugar-containing polymers in the retina are being studied to determine what role sugars play in the transport and assembly of rhodopsin into disc membranes.

(2) Experimental Embryology. The goals of this section are to identify and characterize the myriad tissue interaction that controls the orderly growth of the vertebrate eye and to assure that each ocular part develops a size, shape, and orientation appropriate to its function in this sense organ. Researchers are determining which tissues are responsive to such influences, the duration of these potencies and competencies during embryogenesis, the species and tissue specificities of these interactions, and the nature of these tissue interactions which control morphogenesis.

Because most congenital defects of the eye are attributable to interference with these interactions, identification and characterization is considered indispensable to establishing the etiology of most congenital eye defects. In particular, attention is being focused on newly-discovered,

cell-free, collagen containing "interior layers" that are transiently produced by several epithelia of the embryonic eye and thought to be directly involved in the differentiation and morphogenesis of most organs of the body.

(3) Experimental Pathology. Research being conducted in this section of the laboratory centers on anatomic and pathologic studies of ocular tissue. Studies of the effects of intraocular pressure on eye tissue, the damaging effect of light on the retina, laser effects on the retinal blood vessels, and the pathology of glaucoma are among current projects.

(4) Neurophysiology. Investigations in this section are currently underway to better understand the cellular organization underlying visual perception in both health and disease. Studies are being conducted on the responses of single nerve cells in the visual nervous system of the rhesus monkey. The purpose of this work is to understand how each nerve cell functions in contributing to visual sensations such as color, shape, movement, depth, etc. The technique employs fine glass micro-electrodes which can be inserted into the brain in order to record from single nerve cells. It uses refined optical methods to enable an experimenter to observe the retina while stimulating it with punctate spots or lines of colored lights whose movement and shape can be quantitatively controlled. It requires electrophoresing particles of dye into single cells whose responses have been studied and then finding these particles precisely within the brain after the animal is sacrificed.

Studies in the rhesus monkey striate cortex, which have indicated that visual information processing by the brain involves feature detection rather than photographic reproduction, also include investigations of retinal function at the cellular level. The goal is to better understand vision and pathophysiology of retinal disease. Deeper understanding of abnormal states in the cellular physiology of the mammalian retina is also expected to emerge from studies in this section.

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National Heart and Lung Institute

Donald S. Fredrickson, M.D., Director of Intramural Research
Frederic C. Bartter, M.D., Clinical Director

Associate Program in Medicine, Surgery, and the Basic Sciences

The National Heart and Lung Institute currently appoints three Research Associates and six Clinical Associates in Medicine for a 2-year period beginning each July 1. Several Staff Associates are also appointed in one or more of the Institute's laboratories. For those who are interested in lengthening their period of research experience, these appointments may usually be extended, by mutual agreement, for a third year. Five Clinical Associates are also appointed for 2-year periods in Surgery.

Research and Clinical Associates in Medicine

Candidates for Research and Clinical Associate positions have only one interview in the Heart and Lung Institute. Each Associate who is chosen is free to select his own area of research assignment. After his appointment and prior to his entering on duty, he will make a separate visit, at Institute expense, to select the laboratory in which he will work. The choice is based on the background and interests of the Associate and appointment to the chosen laboratory is contingent only on the ability of that particular laboratory to furnish proper supervision and facilities. (On the basis of past experience, it appears virtually certain that each Associate will be able to work with the group of his choice.) The level of research responsibility and freedom will depend upon his training and experience as well as his desires.

Each Associate in Medicine will devote his time primarily to research in the laboratory under the immediate supervision of a preceptor in an area of his selection. Each is expected to engage in appropriate course work in the basic, medical, and allied sciences as well as tutorial seminars, and to take an active part in the journal club and other exercises of his laboratory.

Research Associate. These appointments are designed to give physicians an opportunity to improve their background for a career in basic medical research. Usually physicians enter the appointment after completing internship and 1-year residency, but there are no specific requirements for postgraduate training after the M.D. degree. No clinical assignments are involved (unless the Associate has chosen a laboratory involved directly in clinical investigation), but the Associates are welcome to attend any of the clinical teaching exercises.

Clinical Associates. These appointments are designed to give physicians training in both clinical and basic research. Candidates must have completed a minimum of 1 year of internship plus 1 year of residency in internal medicine by the starting date of their appointment.

Clinical Associates will be responsible, under the guidance of investigators on the Heart and Lung Institute staff, for the medical care of patients during 8 of the first 12 months of their service. During this time they will rotate through the three medical services that serve the clinically oriented branches of the Heart and Lung Institute. These services occupy 75 beds and include: (1) Cardiology, (2) Endocrinology-Hypertension, and (3) Metabolism, Hematology and Lung.

The clinical period is one of intensive training under direction of the Clinical Director and staff. It offers exposure to case material of an extraordinary range and to highly sophisticated approaches to investigation of disease.

The Clinical Associate devotes both his time off the wards and a full 16 months of his 2-year assignment to laboratory research under direction of a preceptor *in any one of the Heart and Lung Institute laboratories, either clinical or nonclinical.* No clinical responsibilities are required during the optional third year for Associates who have chosen nonclinical laboratories.

Staff Associates. Laboratories within the Heart and Lung Institute sometimes have openings for Staff Associates appointed from the Matching Program. When such appointments are available they are listed in the Program Area Selection Check List for the Institute. Selections for those positions are made by the Chief of the Laboratory. The position of Staff Associate is otherwise comparable to that of Research Associate.

Clinical Associates in Surgery. The Surgery Branch of the National Heart and Lung Institute appoints approximately five Associates in Surgery for a 2-year period beginning each July 1. The program is primarily designed for young surgeons with primary interests in cardiovascular surgery and cardiovascular physiology. In making appointments, preference will be given to candidates contemplating a career in a research or academic atmosphere. Candidates must have completed an internship and at least 1 year of surgical residence by the starting date of their appointment.

Staff Associate in Epidemiology. The Epidemiology Branch conducts population-based studies on the occurrence and natural history of cardiovascular, cerebrovascular, blood, and obstructive pulmonary diseases in general and selected populations in the United States and foreign countries. Through clinical examinations and analyses of available data, these studies seek to improve knowledge of the personal, environmental and familial factors underlying these disorders. One or two candidates are chosen each year for 2-year assignments in Bethesda or one of the field

programs. The Associateships may begin after internship or after 1 year of training in a clinical residency or school of public health. Candidates interested in this possibility are encouraged to write Dr. Manning Feinleib, Chief, Epidemiology Branch, National Heart and Lung Institute, Bethesda, Md. 20014, for more detailed information about specific assignments.

Joint Endocrinology Training Program. Beginning July 1, 1973, Clinical Associates from the National Heart and Lung Institute may participate in a 3-year joint Endocrinology Training Program. The aim of the program is to provide clinical and research experience in a wide variety of endocrine and metabolic diseases and to qualify associates for the Endocrinology Subspecialty Boards. National Heart and Lung Institute participants will spend 6 months in full-time clinical activity consisting of 3-month rotations on the endocrine services of the National Institute of Arthritis, Metabolism, and Digestive Diseases and the National Institute of Child Health and Human Development. During this 6-month clinical period, the Associate will function as a primary care physician for inpatients, see consultations, and participate in outpatient work, rounds and seminars. The remainder of the Associate's 3 years will be spent primarily in research activity within the National Heart and Lung Institute, although he will be expected to continue participation in outpatient work and rounds. National Heart and Lung Institute Associates wishing to participate in this program must state their intention 1 year before entering on duty, and obtain permission from their laboratory chiefs. In general, it will not be possible for more than two Associates to enter this program in any 1 year. Applicants desiring details concerning this program may consult Bruce Weintraub, M.D., Coordinator of Endocrinology Training Program, Clinical Center, Room 9S261, Bethesda, Md. 20014.

Formal Instructions

The major form of didactic postgraduate instruction is through the evening courses offered by The Graduate Program of the Foundation for Advanced Education in the Sciences, Inc., and through the NIH tutorials. Research, Clinical, and Staff Associates are expected to take advantage of this academic work.

Laboratories, Branches, and Sections

The laboratories, branches, and sections of the National Heart and Lung Institute, all of which are open to Clinical and Research Associates for their research work, are listed below with the names of their chiefs and a brief summary statement indicating the breadth of activities. Candidates desiring further information may obtain a current bibliography summarizing the activities of the current staff by writing to Dr. Donald S. Fredrickson, Director of Intramural Research, National Heart and Lung Institute, Bethesda, Md. 20014.

Section on Experimental Atherosclerosis (Head, Dr. Donald L. Fry). The section program is directed toward experimental evaluation of the pathological, physiological, biophysical, chemical and histological processes involved in the genesis of atherosclerosis. These studies are carried out with tissues from both animal colonies and human subjects.

Section of Pathology (Head, Dr. William C. Roberts). This section is concerned with the study of morphologic aspects of cardiovascular disease and their correlation with functional derangements. Morphologic analyses include electron microscopy.

Section on Theoretical Biophysics (Head, Dr. John L. Stephenson). The primary interest of this section is the theory of transport processes in biological systems, with particular reference to problems in cardiovascular, renal, and membrane physiology. The section is concerned both with the formulation of theoretical models and with the development of mathematical and computational methods for their analysis. Currently much of the research in the section centers on the mechanism of urine formation in the mammalian kidney.

Laboratory of Biochemical Genetics (Chief, Dr. Marshall Nirenberg).

Section on Molecular Biology (Head, Mr. Marshall Nirenberg). This section is primarily concerned with basic biochemical studies pertaining to the transfer of genetic and neural information, i.e., genetic programs for differentiation that determine informational reactions of neuron. Systems and problems involve the culture of mammalian cells and hybrid cells, and gene function, for informational molecules, such as enzymes of transmitter metabolism receptors, membrane ionophores, cyclic nucleotides, and other components required for cell recognition and communication.

Section on Somatic Cell Genetics (Head, Dr. John D. Minna). The function, regulation, and organization of mammalian genes related to development and differentiation are studied in health and disease with the use of somatic cell hybridization techniques.

Section on Macromolecules (Head, Dr. Alan Peterkofsky). Studies of regulatory mechanisms involved in nucleic acid and protein biochemistry. Current emphasis is on regulation of cyclic AMP metabolism in microbial systems as well as mammalian protein synthesis.

Laboratory of Biochemistry (Chief, Dr. Earl R. Stadtman).

Section of Enzymes (Head, Dr. Earl R. Stadtman). Studies of diverse enzyme systems that offer unique opportunities to elucidate a number of basic biochemical phenomena, namely, those concerned with vitamin-coenzyme function, the cellular regulation of

metabolism, the energy-dependent transport of metabolites across membrane barriers, and mechanisms of enzyme action.

Section on Cellular Physiology (Head, Dr. Wayne Kielley). This section conducts studies of the structural basis for the biochemical properties of protein molecules and their integrated function in cellular structures. Primary emphasis is on muscle contraction and other motile systems.

Section on Cellular Biochemistry and Ultrastructure (Head, Dr. Edward D. Korn). This section studies structure-function relationships at molecular and cellular levels. Present activities are focused on the biochemistry of the plasma membrane in relation to endocytosis and the molecular and ultrastructural basis of cell motility. Opportunities are available for research and training in biochemistry and electron microscopy.

Laboratory of Chemical Pharmacology (Chief, Dr. James R. Gillette).

Section of Clinical Pharmacology. This section explores mechanisms of idiosyncratic effects of drugs. Also explores biochemical and physiological mechanisms of drug action, including the functions of the autonomic nervous system, the role of adrenocortical, thyroid and other hormone systems in regulating the autonomic and central nervous systems and the processes that control the tissue levels of biogenic amines, acetycholine, and c–AMP.

Section on Physiology (Head, Dr. Harriet M. Maling). This section studies interactions of drugs, particularly the mechanisms by which various pretreatments may alter the hepatotoxicity induced by organic compounds. This includes study of how hepatotoxicity may be correlated with changes in the covalent binding of metabolites to liver lipids and proteins, changes in diene conjugation of microsomal lipids and the formation of lipid peroxides, and effects on microsomal enzymes. The roles of vasoactive substances and the autonomic nervous system in the production of edema and inflammatory reaction are also under study.

Laboratory of Chemistry (Chief, Dr. Henry M. Fales). Conducts research into methods for the structural analysis of organic compounds specifically *via* mass spectrometry, X-ray crystallography, nuclear magnetic resonance, etc., in addition to classical methods of chemical degradation. Also studies biosynthetic pathways *via* tracer techniques and chemical synthesis.

Laboratory of Kidney and Electrolyte Metabolism (Chief, Dr. Jack Orloff).

Section on Electrolyte Transport (Head, Dr. Jack Orloff).

Section on Renal Mechanisms (Head, Mr. Maurice B. Burg).

Section on Membrane Metabolism (Head, Dr. Joseph S. Handler).

Section on Experimental Cardiovascular Diseases (Head, Dr. Stephen Hajdu).

This laboratory conducts research on the mechanism and regulation (hormonal and otherwise) of a variety of transport processes in systems including the intact kidney, isolated perfused segments of renal tubules, toad bladder, erythrocyte, and muscle. Electrophysiology and intermediary metabolism as related to transport are emphasized.

Laboratory of Technical Development (Chief, Dr. Robert L. Bowman). Conducts research into instrumentation and methodology applicable in heart and biomedical research. The scope of the program extends from highly specialized research ultramicro methods to practical clinical instrumentation.

Section on Pulmonary and Cardiac Assist Devices (Head, Dr. Theodor Kolobow). Conducts a program to develop and clinically apply devices for extracorporeal support of the respiratory and circulatory systems. This program includes the development of improved blood oxygenators, blood pumps, and control systems.

Cardiology Branch (Chief, Dr. Stephen E. Epstein).

Section on Cardiovascular Diagnosis (Head, Dr. David R. Redwood). Investigations are oriented toward the diagnosis of acquired and congenital heart diseases, the evaluation of operative and nonoperative forms of treatment, and the elucidation of mechanisms responsible for the hemodynamic changes produced by heart failure.

Section on Cardiovascular Pharmacology (Head, Dr. Theodore Cooper). Current work is concerned with a comprehensive study of the terminal nervous innervation of the heart and how it influences electrical stability of the ventricle. Cellular effects of drugs are also under investigation in isolated cardiac tissue. The action of antiarrhythmic agents under conditions of myocardial ischemia is under investigation.

Section on Clinical Physiology (Head, Dr. Stephen E. Epstein). Research objectives are aimed towards an understanding of the physiologic, anatomic and biochemical mechanisms responsible for control of the normal heart and circulation, an elucidation of the alterations produced by ischemic and nonischemic heart disease, and an evaluation of interventions designed to reverse the biochemical and, thereby, the physiologic aberrations of function. Several approaches are being employed to achieve the above, including hemodynamic and echocardiographic (one- and two-dimensional systems) studies in man, electron microscopic and biochemical

studies of tissues obtained from human surgical specimens as well as from the experimental animal, and pharmacologic investigations in man and animals.

Section on Molecular Cardiology (Head, Dr. Robert S. Adelstein). Current investigations are directed toward an understanding of the function and control of the contractile proteins of heart, blood platelets and other cells (both muscle and nonmuscle). Projects include: (a) the role of cyclic AMP and phosphorylation in the regulation of contractile protein function, (b) the characterization, on a molecular level, of the contractile proteins found in disease states such as asymmetric septal hypertrophy (ASH) and those characterized by congestive failure.

Hypertension-Endocrine Branch (Chief, Dr. Frederic C. Bartter).

This branch represents a merger of the previous Endocrinology and Experimental Therapeutics Branches. A major emphasis is on research related to hypertension, but its activities are wide-ranging, as indicated by the description of section activities.

The principal research of this branch is directed towards the pathophysiology of hypertension. It is broadly approached through clinical, physiological, and biochemical studies on steroid metabolism, on the renin-angiotensin system, on the kallikrein-kinin system, on the sympathetic nervous system, including catecholamines, on prostaglandins, and on the interrelations of each of the above with mineral metabolism and the kidney.

In addition, the following two clinical sections are involved in other research as described below.

Section on Experimental Therapeutics (Head, Dr. Harry R. Keiser). A wide spectrum of research opportunities is offered, ranging from basic biochemistry and pharmacology to the study of chemical factors in disease and clinical response to drugs. Other current studies encompass disorders of serotonin and histamine, and of collagen metabolism and studies in the biochemistry of sleep.

Section on Steroid and Mineral Metabolism (Head, Dr. Frederic C. Bartter). Other research of this section involves the functions of the adrenal glands, the parathyroid glands, the pituitary glands, and their interrelationships with the kidneys, studies on metabolic bone disease and metabolism and on the pathogenesis of nephrolithiasis, and studies on a wide variety of other endocrine disorders. There is strong emphasis on chronobiology and chronopharmacology.

Section on Biochemical Pharmacology (Head, Dr. Walter M. Lovenberg). This section conducts a broad research program on the molecular mechanism of neuronal function. Studies relate primarily

to the properties and regulation of the enzymes responsible for the biosynthesis of neurohormonal amines. The role of these systems in disease states, particularly hypertension, is a prime objective and investigations are extended from the molecular level to experimental animals and man.

Section on Neuroendocrinology (Head, Dr. Robert I. Henkin). Research is devoted to the study of the interrelationships between the nervous and the endocrine systems in three interrelated areas: (1) the effects of steroid hormones on nervous system activity as well as steroid localization and metabolism in the nervous system; (2) mechanisms of function of gustation, olfaction and audition as represented in various disease states; and (3) the effects of trace metals in neuroendocrine metabolism, in various altered metabolic states and as indicators and treatment in various gustatory and olfactory abnormalities.

Section on Physiological Chemistry (Head, Dr. John J. Pisano). Normal and pathologic states in man are studied at the molecular level by advanced analytical techniques. Under investigation are the prostaglandins and vasoactive peptides (e.g., bradykinin and angiotensin), precursor proteins of the peptides and the enzymes involved in their biosynthesis and degradation. Research is currently directed to the study of hypertension, coagulation and fibrinolysis.

Molecular Disease Branch (Chief, Dr. Donald S. Fredrickson). The activities of this branch are concerned primarily with the metabolism and transport of lipids. This includes the structure and relationships of lipoproteins and their apoprotein constituents, and the nature of enzymes involved in fat metabolism and the regulations of their activities, particularly as they control the concentrations of lipids in plasma and tissues. A major interest is dyslipoproteinemia and other metabolic diseases, especially those which are genetically determined, and related to lipid transport, metabolism and to atherosclerosis. The Section on Metabolism (Dr. Martha Vaughan) is autonomous; the activities of the others are integrated in such a way that, if they wish, Associates may participate in collaborative work involving several sections.

Section on Metabolism (Head, Dr. Martha Vaughan). Major areas of research interest are: (1) the mechanisms underlying hormonal control of lipolysis in fat cells, with emphasis at present on characterization of the hormone-sensitive lipase and elucidation of the manner in which insulin, prostaglandins, and adrenal steroids affect the formation, degradation, and action of cyclic AMP; and (2) the role of cyclic AMP, cyclic GMP, and compounds that influence the metabolism of these nucleotides (e.g., prostaglandins,

adrenal steroids) in regulation of growth and morphology of mammalian cells grown in culture.

Section on Genetics and Lipid Biochemistry (Head, Dr. Howard R. Sloan). Research includes studies of the structure and function of complex lipids, tissue culture, tissue lipid hydrolases, and lipid and lipoprotein analysis.

Section on Peptide Chemistry (Head, Dr. H. Bryan Brewer). Research is directed toward the analysis and synthesis of polypeptide hormones and lipoproteins with the object of developing knowledge of structure-function relationships.

Section on Lipoprotein Structure and Functions (Coheads, Dr. Peter Herbert and Dr. Richard Shulman). Research is concerned with isolation, identification and structure of apolipoproteins, and elucidation of their special functions and interrelationships. Section on Lipoprotein Metabolism (Head, Dr. Robert I. Levy). Research is on the kinetics and mechanisms of plasma lipoprotein turnover. This section also includes the staff conducting the National Heart and Lung Institute's Type II Intervention Study (Coordinator, Dr. John F. Brensike).

Section on Molecular Diseases (Head, Dr. Donald S. Fredrickson). This section is concerned with the integration of lipid transport and metabolism, especially alterations resulting from genetically-determined disease.

Molecular Hematology Branch (Chief, Dr. W. French Anderson).

This branch is concerned with investigations into the mechanism and regulation of mammalian gene expression and protein synthesis, specfically relating to hemoglobin and to diseases involving the regulation of hemoglobin synthesis.

Section on Molecular Genetics (Head, Dr. W. French Anderson). This section conducts investigations into the mechanism and regulation of hemoglobin biosynthesis. Studies includes cell-free hemoglobin synthesis directed by isolated mRNA, globin mRNA transcription from bone-marrow chromatin, and attempts to synthesize a DNA gene coding for globin mRNA with the use of the enzyme reverse transcriptase.

Section on Clinical Hematology (Head, Dr. Arthur W. Nienhuis). Application of the techniques of cell and molecular biology aimed at the understanding and treatment of human disorders of hemoglobin synthesis and erythroid differentiation. Major research areas include: regulation of mRNA and hemoglobin synthesis in intact cells, bone marrow tissue culture, and somatic cell hybridization. Patients with a broad range of red blood cell diseases are studied on the clinical service.

Pulmonary Branch (Acting Chief, Dr. Claude J.M. Lenfant).

This branch is newly formed and is in the process of development and expansion. It represents a focus for much of the Institute's intramural research on the lung and is designed particularly to approach the physiology and diseases of respiratory tissue through molecular biology. Both laboratory and clinical investigations are conducted. The laboratory presently has three sections.

Section on Lung Biochemistry (Head, Dr. Ronald Crystal). Investigation of the molecular basis of lung function in health and disease using techniques of molecular biology and tissue culture with specific emphasis on the regulation of synthesis of collagen and other proteins in the lung.

Section on Pulmonary Physiology. The section is directed toward evaluation of the physiological processes in health and diseases. Findings are correlated with molecular biology and morphology observations. Studies are carried out in human and experimental models.

Section on Molecular Pharmacology (Head, Dr. Elwood O. Titus). Studies the mechanisms by which neurohumoral transmitters, hormones and drugs affect pulmonary and cardiovascular function. Activities include the characterization of cellular receptors for drugs and hormones as well as studies of the ionic mechanisms underlying signal transmission from nerve to muscle. Considerable emphasis is placed on the use of physical methods such as optical rotatory dispersion, fluorescence, nuclear magnetic resonance and electron spin resonance for the study of drug protein interactions.

Surgery Branch (Chief, Dr. Andrew G. Morrow).

National Institute of Allergy and Infectious Diseases

John R. Seal, M.D., F.A.C.P., Scientific Director

Sheldon M. Wolff, M.D., F.A.C.P., Clinical Director

The NIAID annually appoints Associates for the Laboratories described below. Clinical Associates are selected by the Clinical Director, are appointed to the Laboratory of Clinical Investigation, and begin after one year of residency training. Research Associate appointments in the other laboratories may begin after internship or residency training. In general, those appointments which begin after one or more years of residency training have some degree of responsibility for human subjects in the research program but are not otherwise different from those which begin after internship.

Appointees through the Early Commissioning Program will be regarded as appointees through other programs and final identification as to positions for which they are being considered and as to whether or not the position will afford one or more years of residency training before entry will be made to perspective candidates at the time of interview.

Specific answers may be obtained for any questions or additional information obtained by applicants from Dr. John R. Seal, Scientific Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md. 20014. This can include rosters of scientific staff, summaries of research, or information about possible opportunities not listed under the laboratories. In writing, please be as specific as possible as to interests of applicant and information desired.

The Laboratory of Clinical Investigation (Sheldon M. Wolff, M.D., Chief).

The National Institute of Allegry and Infectious Diseases appoints six to eight Clinical Associates. Appointments are made for 3 years. Ward medical care duties occur during the first year, and no assigned clinical responsibilities are made during the second or third year except as dictated by the needs of the Clinical Associates' research.

There are 52 research beds. Clinical Associates consult on clinical infectious disease problems in other Institutes and at the National Naval Medical Center. Each Clinical Associate selects his own area of investigative interest under the general preceptorship of the Clinical Director and the senior members of the staff of the Laboratory of Clinical Investigation. Emphasis is placed on the conduct of laboratory and clinical research designed to provide the basic training necessary for a career in

clinical investigation. The third year is credited towards a year of fellowship training by the allergy and immunology specialty board of the American Board of Internal Medicine.

Opportunities exist for research in a wide variety of areas of infectious and immunological disease. Examples of studies now in progress are:

- The etiology and pathogenesis of certain viral infections in man.
- The role of certain host defense mechanisms in prevention of infections.
- Pathogenesis and treatment of granulomatous diseases.
- Cellular immunity and delayed hypersensitivity in systemic mycoses.
- Pathogenesis of both experimental and clinical fevers.
- The role of the granulocyte in resistance and response to infection.
- Mechanisms of immune damage and the role of complement in immunological reactions.
- The biochemical response in lymphoid cells following antigenic stimulation in normal and immunologically impaired subjects.
- The pathogenic mechanisms of the aspirin sensitivity-asthma syndromes.
- The structure and function of immunoglobulins of human and lower animal origin.
- The application of electron microscopy, autoradiographic, and cytochemical techniques to studies of cellular interactions in immunologic information processing both in humoral and cellular events.
- The interrelationship of coagulation and fibrinolysis to kinin generation and the role of these enzymatic pathways in the pathogenesis of reactions of the immediate hypersensitivity type.
- Research in both the clinical and laboratory aspects of parasitic diseases.
- The pathogenesis of cold urticaria, cholinergic urticaria, and chronic idiopathic urticaria and angioedema.
- The effect of corticosteroids and cytotoxic agents on lymphocyte subpopulations.
- Study of chronic bacterial pulmonary infections.

Further information can be obtained if inquiries with specific questions are addressed to Dr. Sheldon M. Wolff.

The Laboratory of Viral Diseases (Wallace P. Rowe, M.D., Chief) conducts research on the basic biology and ecology of chronic and persistent virus infections, with particular emphasis on oncogenic viruses, and on host antiviral defense mechanisms.

Studies of tumor viruses are concentrated on murine leukemia viruses, SV40, adenovirus-SV40 hybrod viruses, and Marek's disease of chickens.

These studies include investigations of the interactions between defective and competent viruses, etiology of naturally occurring animal tumors, serologic characterization of viral products, and genetics of the viruses.

The mechanism of action of interferon and inducers of interferon is studied by biological and biochemical approaches. The laboratory will be participating in clinical evaluation of interferon inducers in a variety of diseases.

The Laboratory of Biology of Viruses (Norman P. Salzman, Ph.D., Chief) is primarily concerned with the molecular events involved in virus replication. Investigations are also conducted to define the basis for the pathogenic effects of viruses on cellular functions. Biosynthesis of the nucleic acid, protein and carbohydrate components of virus particles and factors governing their assembly are under study as is the mode of action of certain specific antiviral substances. These studies are carried out with both lytic and oncogenic viruses. The mechanisms by which normal cells are transformed to an oncogenic state is an important area of investigation. Fundamental biochemical and biophysical studies are also carried out with uninfected cells.

Parallel studies to those on viral synthesis seek to define the physical and chemical makeup of the purified virus itself, utilizing electron microscopy, ultracentrifugation, and nucleic acid and protein analysis.

Other programs investigate the isolation and characterization of mutated viruses. Studies are conducted on the relationship between mutations in the viral genome and biochemical alterations in the infectious cycle.

The staff includes persons trained in biochemistry, medicine, microbiology, physical chemistry, and organic chemistry. The program for associates is designed to provide them with a full understanding of modern trends in molecular biology and to enable them to apply biochemical and biophysical methods in dealing with fundamental problems in virology, cell biology and medicine.

The Laboratory of Infectious Diseases (Robert M. Chanock, M.D., Chief) is concerned with the basic behavior of viral and mycoplasmal pathogens which play an important role in acute infectious diseases of man. The importance, disease manifestations and ecologic properties of various respiratory tract pathogens are defined during the study of individuals with naturally acquired disease. Supplementary information is obtained from detailed investigation of experimentally infected volunteers in an attempt to define the pathogenesis of disease and the factors involved in the hosts' resistance to both infection and illness. The techniques of microbial genetics are employed to study the nature of virulence and to select attenuated mutants which are then evaluated for their usefulness in vaccination against natural disease.

Biophysical techniques are used to define the subparticulate structure of

viruses and to search for certain fastidious agents, such as coronaviruses and hepatitis viruses, which cannot be detected in standard tissue culture systems. Appointees can expect to receive training in basic biophysical and biological characterization of viruses and mycroplasmas, microbial genetics, immunologic methods used in the study of respiratory tract disease and epidemiologic techniques employed in defining the ecology of agents which cause actue infectious diseases. Some appointments are made for 3 years.

The Laroratory of Immunology (William E. Paul, M.D., Chief) is engaged in the study of various aspects of cellular immunology, immunogenetics and immunochemistry, particularly as they bear on a fuller understanding of the biological signficance of the immune response and on the role of immune mechanisms in both the prevention and pathogenesis of human diseases.

Areas of active investigation now include the study of the origin, development, functional diversity and mechanisms of activation of lymphocytes; the genetic control of specific immune responses and of interactions between immunocompetent cells; the nature and specificity of antigen-binding receptors of lymphocytes; the chemistry of allotypic determinants of rabbit and mouse immunoglobulins and the use of such determinants to study the genetic control of immunoglobulin synthesis; and the degree of specialization of individual immunocompetent cells.

Further, active study of the role of different lymphocyte classes in a variety of human diseases are underway and models for the study of the role of cellular immune responses in tumor immunity and for the investigation of immunotherapy of tumors are being developed.

Associates will have the opportunity to participate in studies in one (or more) of these areas under the preceptorship of one of the senior members of the laboratory. In the course of their work, appointees should receive a thorough grounding both in conceptual and technical aspects of immunology.

The Laboratory of Microbial Immunity (Richard Asofsky, M.D., Chief) is primarily concerned with the elucidation of basic mechanisms involved in both the cellular and humoral immune responses to microbial and tissue antigens.

Several major areas of investigation, each employing a wide variety of immunological methods, offer the associate comprehensive exposure both to the theoretical and to the technical aspects of immunology. Mechanisms of induction, control and ontogeny of immunoglobulin synthesis are being examined in detail. The significance of interaction among different kinds of lymphoid cells in the induction and manifestation of immunity is being studied in graft-versus-host reactions and in humoral immune responses. The development, distribution and susceptibility of the interacting components to various treatments which suppress or

amplify immune reactions are being examined. Methods have been developed for the physical fractionation of lymphoid cells to obtain functionally purified subpopulations. Autoimmune phenomena are studied using allergic thyroiditis and retinitis as models. Factors regulating the development and severity of disease and specific methods of preventing or ameliorating disease are investigated. The nature of the immune response to protozoal parasites, including the antigenic and genetic requirements for the expression of this immunity are studied. In most of the program areas outlined, work *in vivo* is complemented by the use of *in vitro* models.

The Laboratory of Parasitic Diseases (Franklin A. Neva, M.D., Chief) is engaged in both basic and applied studies of parasitic diseases of man. At Bethesda basic research is conducted with organisms such as Toxoplasma, trypanosomes, Leishmania, schistosomes, amebae, and Filariids. For example, current projects include studies of the ultrastructure of parasites, comparative biochemical mechanisms of energy transfer, and *in vitro* host-parasite interactions at the cellular level, utilizing specialized optical techniques. Applied studies include the investigation of experimental parasitic infections as laboratory models, and as naturally occurring infections in man. Currently these studies involve schistosomiasis, filariasis, amebiasis, and Chagas' disease. Collaboration with the Laboratory of Clinical Investigation, provides the opportunity to study patients in the Clinical Center.

The research program on malaria covers many different aspects of the subject including chemotherapy, immunology, pathophysiology, biology of both human and simian malarial parasites, and work with arthropod vectors. An insectary and facilities for work with primates provides unique opportunities for studies on all stages of the life cycle of the organism. The Pacific Research Section in Hawaii (under the direction of Dr. Leon Rosen) conducts research on parasitic as well as vector-borne viral diseases of particular importance to the Pacific area. The isolated ecologic environment of some of the Pacific Islands is utilized for epidemiologic investigations. Current areas of study include dengue hemorrhagic fever and other arboviruses, toxoplasmosis and related coccidia and eosinophilic meningitis.

The Laboratory of Streptococcal Diseases (Roger M. Cole, Ph.D., M.D., Chief) investigates the genetics of streptococci and their bacteriophages, particularly in relation to ultrastructure, cell wall and surface composition, antigenic structure, competence, and autolytic enzymes. Current studies utilize phage-mediated transduction in group A streptococci; and transduction, DNA-mediated transformation and transfection, and lysogenization in group H streptococci. Present efforts are directed to genetic transfer of natural characteristics (i.e., other than antibiotic resistance) which may alter epidemiological patterns in human

disease. Emphasis is on surface antigens which can, if changed, result in differences in virulence, immunogenicity, phage susceptibility, adherence, and serologic recognition.

After review with the Laboratory Chief, associates may elect to pursue basic laboratory studies in any of the above subject areas. Microorganisms other than streptococci may be utilized, when pertinent to demonstration of broad principles under study.

The Rocky Mountain Laboratory (Herbert G. Stoenner, D.V.M., Director) located at Hamilton, Mont., is internationally recognized for research on rickettsial and tick-borne diseases. The laboratory is a WHO Reference Center for Human Rickettsioses. In medical entomology and acarology, principal projects include biology and systematics of ticks and mites, ecology of selected tick- and mosquito-borne viruses, and general and subcellular relationships between arthropod-borne microbiota and their vectors as studied by various approaches, including arthropod tissue culture and electron microscopy.

Various aspects, particularly immunology and microbiology, of selected infectious diseases are under investigation. Scrapie and progressive pneumonia of sheep, and Aleutian disease and encephalopathy of mink are studied as models of chronic degenerative diseases of man. Limited studies are made on pertussis, rabies, tularemia, and the PLT group of organisms. More basic inquiries are made into fundamental mechanisms in delayed hypersensitive, cell-mediated immunity, and antibody production according to immunoglobulin class.

The fractionation of microbial agents, such as *Mycobacteria, Bordetella,* and Gram-negative organisms, by special biophysical and biochemical methods and the role of these subcellular fractions in immunity, hypersensitivity, tumor immunology, and other host responses are subjects of major investigations.

Opportunities for training associated with these research projects are provided in comparative pathology, electron microscopy, scanning electron microscopy, virology, immunology, immunochemistry, and a wide variety of specialized biophysical and biochemical methodology.

National Institute of Arthritis, Metabolism and Digestive Diseases

J. E. Rall, M.D., Ph. D., Director of Intramural Research
Robert S. Gordon, Jr., M.D., Clinical Director

Clinical Associates

The NIAMDD activates about 10 new Clinical Associates each year. The assignments are for 2 or 3 years and usually are not extended. A single position of Senior Associate is open each year and is ordinarily filled from among Clinical Associates completing the regular associateship in NIAMDD.

Each Clinical Associate is attached for his 2- or 3-year period to one of the clinical branches or sections, within which he carries out both clinical work and laboratory studies. He is, in effect, an apprentice clinical investigator, working both on the wards and in the laboratory under the guidance of an experienced preceptor. The Associate is encouraged to choose his own problem for independent investigation, subject to the limitation that the facilities required for its successful pursuit, and the technical advice and supervision necessary, must be available to the branch or section in which he is to be working. In addition, he provides professional care for the research patients admitted to the service of his branch chief, and assists in the work of that branch in the outpatient department. There is considerable variation among the branches of NIAMDD with respect to the proportion of the Associate's time required for patient care activities.

Clinical Associates of the Clinical Endocrinology Branch and the Metabolic Diseases Branch will participate in a 3-year Inter-Institute Endocrinology Training Program which will satisfy requirements for Endocrinology Subspecialty Board Examinations. In certain instances, when positions are available, other NIAMDD Clinical Associates may also spend a third year in the Endocrinology Program.

Since appointments are for at least 2 years, vacancies do not necessarily occur within each program area each year. The chiefs of branches or sections having openings for new Clinical Associates, and the Clinical Director, screen applications and select candidates for personal interviews. After interviews are completed and the results of matching are announced, each successful candidate is asked to confirm his acceptance of the position with which he was matched. It is not possible, after this, to change the Associate's assignment within NIAMDD.

The list below identifies all of the clinical research branches within NIAMDD, and their sections, by title and by the name of the chief.

The Program Area Selection Check List indicates those having vacancies to be filled at this time. Prospective applicants who are not familiar with the qualifications and research accomplishments of the branch and section chiefs, or with the details of their current investigative and clinical programs, are encouraged to write Dr. Robert S. Gordon, Jr., Clinical Director, NIAMDD, Building 10, Room 9N–222, Bethesda, Md. 20014. Supplementary information sheets on each branch, together with selected bibliographic citations, are available on request.

Clinical Associates in Experimental Pathology

In addition to Clinical Associates who take care of patients on wards in the Clinical Center, the Laboratory of Experimental Pathology has clinical responsibility for surgical and autopsy material. This Laboratory appoints approximately two Clinical Associates in Experimental Pathology each year. Further information can be obtained from Dr. Gert L. Laqueur, Chief of the Laboratory of Experimental Pathology.

Staff Associate in Epidemiology

One or two candidates are chosen each year for a 2-year assignment studying the epidemiology of chronic disease (diabetes, arthritis, cholelithiasis, etc.) among the Pima Indians of Arizona. The Associateships begin after internship. Candidates interested in this possibility are encouraged to write Dr. Peter H. Bennett, Epidemiology & Field Studies Branch, NIAMDD, 1440 E. Indian School Road, Phoenix, Ariz. 85014, for more detailed information.

Research Associates

The National Institute of Arthritis, Metabolism, and Digestive Diseases has four positions available each year for Research Associates. These 2-year appointments, usually beginning on July 1, are designed to give highly qualified physicians an opportunity to improve their backgrounds for careers in basic medical research. During his stay here, each Research Associate will devote the larger part of his time to participation in laboratory research under the immediate supervision of a preceptor. The chosen candidates are free to choose a preceptor (upon mutual agreement) in any area in the Institute, either clinical or basic research. Should he elect a clinical area, he would not participate in clinical care of patients. The Research Associate, approximately 1 year prior to beginning, will visit NIAMDD to select the laboratory and preceptor with whom he wishes to work. Candidates desiring further information about the laboratories, staff and bibliography of NIAMDD may obtain this by writing to Dr. J. E. Rall, Director of Intramural Research, NIAMDD, National Institutes of Health, Bethesda, Md. 20014.

Clinical Research Branches

Arthritis and Rheumatism Branch—Dr. John L. Decker

Section on Connective Tissue Disease—Drs. John L. Decker, Paul Plotz, and Alfred D. Steinberg
Section on Human Biochemical Genetics—Dr. Elizabeth Neufeld
Section on Chemical Immunology—Dr. Henry Metzger

Clinical Endocrinology Branch—Dr. Jacob Robbins

Section on Diabetes—Drs. Jesse Roth and Phillip Gorden
Section on Endocrine Biochemistry—Drs. Jacob Robbins, Jan Wolff, Saul Rosen, Hans Cahnmann, Harold Edelhoch, Charles Lewallen, and Bruce Weintraub

Clinical Hematology Branch—Dr. N. Raphael Shulman

Digestive Diseases Branch—Dr. Robert S. Gordon, Jr.

Section on Physiology and Clinical Nutrition—Dr. Robert S. Gordon, Jr.
Section on Gastroenterology—Dr. Jerry D. Gardner
Section on Diseases of the Liver—Dr. Paul D. Berk
Section on Diseases of the American Indian—Dr. Peter H. Bennett, Acting

Metabolic Diseases Branch—Drs. Gerald D. Aurbach and Stephen Marx

Pediatric Metabolism Branch—Dr. Paul A. diSant'Agnese

Basic Research Laboratories

Mathematical Research Branch—Dr. John Z. Hearon

Laboratory of Nutrition and Endocrinology—Dr. Herbert Sober

Section on Nutritional Biochemistry—Dr. John G. Bieri
Section on Endocrinology—Dr. Robert O. Scow
Section on Vitamin Metabolism—Dr. Bernard Kaufman
Section on Developmental Biochemistry—Dr. Herbert Sober
Section on Membrane Regulation—Dr. Martin Rodbell

Laboratory of Biochemistry and Metabolism—Dr. G. Gilbert Ashwell

Section on Enzymes and Cellular Biochemistry—Dr. William B. Jakoby
Section on Intermediary Metabolism—Dr. Yale J. Topper

Laboratory of Experimental Pathology—Dr. Gert L. Laqueur

Section on Histochemistry—Dr. George G. Glenner
Section on Chemical Pathology—Dr. Robert Friedman
Section on Biophysical Histology—Dr. Ned Feder

Laboratory of Biochemical Pharmacology—Dr. Herbert Tabor

Section on Pharmacology—Dr. Herbert Tabor
Section on Biochemistry—Dr. Victor Ginsburg
Section on Biochemistry of Amino Acids—Dr. Simon Black

Laroratory of Chemistry—Dr. Bernhard Witkop

Section on Carbohydrates—
Section on Medicinal Chemistry—Dr. Everette L. May
Section on Biochemical Mechanisms—Dr. Louis A. Cohen
Section on Metabolites—Dr. Bernhard Witkop
Section on Microanalytical Services and Instrumentation—Dr. David Johnson
Section on Pharmacodynamics—Dr. John W. Daly

Laboratory of Physical Biology—Dr. John B. Buck

Section on Comparative Physiology—Dr. John B. Buck
Section on Cellular Physics—Dr. Richard J. Podolsky

Laboratory of Chemical Physics—Dr. Edwin D. Becker

Section on Molecular Biophysics—Dr. Edwin D. Becker
Section on Physiology—Dr. Paul Altland
Section of Spectroscopy and Structure—Dr. Elliot Charney
Section on Membrane Biophysics—Dr. William A. Hagins

Laboratory of Molecular Biology—Dr. Robert Martin

Section on Metabolic Enzymes—Dr. Martin Gellert
Section on Molecular Genetics—Dr. Jun-ichi Tomizawa
Section on Physical Chemistry—Dr. Gary Felsenfeld
Section on Molecular Structure—Dr. David R. Davies
Section on Microbial Genetics—Dr. Robert Martin
Section on Organic Chemistry—Dr. H. Todd Miles
Section on Theoretical Molecular Biology—Dr. Terrell Hill

Laboratory of Chemical Biology—Dr. Christian B. Anfinsen

Section on Protein Chemistry—Dr. Christian B. Anfinsen
Section on Macromolecular Biology—Dr. Alan Schechter

Laboratory of Biophysical Chemistry—Dr. Koloman Laki

Section on Bioenergetics—Dr. David Kominz
Section on Macromolecules—Dr. Harry A. Saroff
Section on Physical Biochemistry—Dr. Koloman Laki

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National Institute of Child Health and Human Development

Intramural Research Program

Charles U. Lowe, M.D., Scientific Director

Griff T. Ross, M.D., Clinical Director

This Institute offers associate training programs in the branches indicated below. These programs include activities appropriate to a variety of specialized backgrounds, including obstetrics and gynecology, pediatrics, neonatology, internal medicine, learning and behavioral biology, as well as physiology, biochemistry, biophysics, reproductive physiology, genetics, pharmacology, psychology, and developmental issues.

The Behavioral Biology Branch (Phillip G. Nelson, M.D., Ph. D., Chief). Conducts electrophysiologic and biochemical studies of the neurobiologic basis for short- and long-term interaction between nerve cells. The central neural mechanism underlying sensory discrimination in primates is studied by electrophysiologic and behavioral techniques.

The Section on Brain and Behavior (David Symmes, Ph. D., Head). Electrophysiologic correlates of sensory coding and discriminative behavior are analyzed using microelectrode computer techniques. Behavioral consequences of brain lesions are studied.

The Section on Neurobiology (Phillip G. Nelson, M.D., Ph. D., Head). Tissue cultured neural and muscle tissue and small *in vitro* vertebrate and invertebrate neural systems are studied electrophysiologically and biochemically. Long-term interactions between neurons and between nerve and muscle are of particular interest.

Developmental Immunology Branch (John B. Robbins, M.D., Chief). In this new program of the Institute the development of immunity in infants and children is being studied utilizing *Hemophilus influenzae* type b disease and its type b capsular polysaccharide as a model system. The immunogenic characteristics of the type b polysaccharide and its protective value following immunization of infants and children is being studied in a field trial. Investigations in the nature of a serologic relation between cell surface structure and type b polysaccharide in individuals with *Hemophilus influenzae* dsease are being conducted to study the susceptibility of non-immune individuals.

Particular emphasis is currently being directed toward establishing the relation between enteric organisms found to possess the cross reacting

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antigens to *H. influenzae* type b and the development of "natural" immunity to diseases caused by this pathogen.

Current plans project an obstetric and newborn delivery program at the Clinical Center. This program will provide an opportunity to study normal perinatal and neonatal adaption to the antigens of the nasopharyngeal and enteric microorganisms.

Gerontology Research Center (Nathan W. Shock, Ph. D., Associate Scientific Director for Gerontology). The multidisciplinary program of the Center, located in a special research building on the campus of the Baltimore City Hospitals, offers Clinical (primarily clinical research) and Staff (primarily basic research) Associate training. Preference is given to candidates who intend to pursue careers in investigative and academic medicine. With appropriate approval, Associates may participate in clinical activities of the Baltimore City Hospitals and the nearby hospitals of the Johns Hopkins University and the University of Maryland. The Baltimore City Hospitals are affiliated with both institutions.

Associates participate in a seminar conducted by the staff of the Center which presents a comprehensive view of research in aging. Weekly research conferences are presented by members of the staff and invited lecturers.

In support of the programs in molecular aging and cellular and comparative physiology the Center maintains extensive animal colonies to provide rats, mice, and house flies, of known ages, including senescent animals. Animal operating rooms are available as well as shops for the design and construction of special equipment. The library of the Center includes standard scientific journals as well as an extensive collection of the literature on aging research.

The Gerontology Research Center is composed of four branches:

The Laboratory of Cellular and Comparative Physiology (Takashi Makinodan, Ph. D., Chief). This laboratory is concerned with the effects of age on cellular differentiation in humans and other mammalian species. Currently, emphasis is placed on immunologic and biochemical evaluations of cells of normal and genetically altered tissues, which are separated according to size, density, membrane receptors, etc. The objectives are to determine the changes caused by alterations of both genetic information and cellular regulation.

Research in immunology is focused on the identification of the humoral and cellular factors responsible for age-associated deterioration of both cell-mediated and humoral immune functions. Research has also been initiated for ways in replenishing the defective immune system of the aged and controlling immunodeficiency diseases prevalent among the aged. An example of the latter is the study recently initiated to assess the long-term effects of caloric and protein undernourishment on the immune system, immunodeficiency diseases and life span. Research in mammalian genetics is focused on metabolic and cellular changes associated with

altered development and aging. Particular emphasis is placed on the relationship between altered nucleic acid and protein metabolic activities of cells and their chromosomal aberrations.

Research in the Cellular Immunology Section (Albert A. Nordin, Ph. D., Chief) is focused on (a) the identification of the humoral and cellular factors responsible for age-associated deterioration of both cell-mediated and humoral activities of the immune system, (b) the search for ways of rejuvenating the defective immune system of the aged, and (c) attempts to prevent and control autoimmune diseases prevalent among the aged.

The Nutritional Biochemistry Section (Charles H. Barrows, Jr., Sc. D., Chief) investigates the relationship between life span, as affected by nutrition, temperature and antimetabolites, and enzymatic activities of tissues of various animals.

The Morphology Section (Dorothy F. Travis, Ph. D., Chief) is concerned with investigating the basic structural and functional activities of highly differentiated, non-renewable myocardial cells and dividing renewable skeletogenic cells as they relate to growth, development, and the aging process.

The Mammalian Genetics Section (Edward L. Schneider, M.D., Chief) is undertaking the study of human and animal disorders manifesting altered development and aging. These studies will be focused on cellular metabolism utilizing tissue culture techniques as well as experimental animal models.

Clinical Physiology Branch (Reubin Andres, M.D., Chief). This branch is primarily concerned with studies on physiological changes occurring during the entire adult age span. Studies include quantitation of age changes, elucidation of mechanisms underlying these changes, and the relation between aging processes and specific disease states. Clinical research is conducted on 600 community-dwelling volunteers who comprise a panel for an extensive longitudinal study of human aging. They spend 2½ days every 18 months on the Gerontology Research Ward in the adjoining Baltimore City Hospitals.

The Endocrine Section (Robert I. Gregerman, M.D., Chief) conducts studies on (a) the enzymology and peptide chemistry of the reninangiotension system and (b) the influence of aging on hormonal responsiveness, especially as related to the adenylate cyclase mechanism.

The Cardiovascular Section (Nathan W. Shock, Ph. D., Acting Chief) investigates cardiovascular hemodynamic function in man using non-invasive methods and in the rat and dog by a variety of experimental techniques.

The Metabolism Section (Reubin Andres, M.D., Chief) conducts research on the kinetics of glucose homeostasis and related endocrine functions using a servo-control technique for clamping glucose levels in man.

The Human Performance Section (Arthur H. Norris, M.A., Chief). This section is responsible for a wide variety of studies on age changes in body composition, pulmonary and exercise physiology, and neuromuscular function.

Laboratory of Behavioral Sciences (Bernard T. Engel, Ph. D., Chief). This program includes studies of the effects of aging on motor behavior, perceptual skills, learning, memory, problem-solving ability, and personality characteristics. These are also studies on the interrelationships among aging and autonomic responses, and the clinical applications of voluntary autonomic control are being investigated. Laboratory facilities exist for measuring cognitive and perceptual functions in man; psychophysiological responses in man; learning and motor behavior in rodents (including selected in-bred strains of mice); learning, cardiovascular and neuropsychological responses in monkeys.

Laboratory of Molecular Aging (Bertram Sacktor, Ph. D., Chief) conducts research on the biochemical control systems in enzyme action and metabolism and on the regulatory processes in molecular biology, with reference to adult development and aging. Studied are mechanisms for regulating glycogenolysis, glycolysis, gluconeogenesis, citric acid cycle activity, and oxidative phosphorylation; renal transport of sugar, amino acids and ions; action of hormones in regulating renal transport and intermediary metabolism; enzyme induction and the biogenesis and turnover of cellular membranes and organelles. Investigated also are the primary and conformational structures of DNA and RNA; the interactions of polynucleotides with each other, metal ions and proteins; cellular uptake of synthetic polynucleotides; polynucleotide hybridization; and the expressions of these interactions in terms of biological function.

The Laboratory of Biomedical Sciences (J. C. Robinson, M.D., Ph. D., Chief) conducts basic research in developmental enzymology, intermediary metabolism, physiological control, and developmental pharmacology.

In the Section on Developmental Enzymology (J. C. Robinson, M.D., Ph. D., Head) primary interest centers on the identification and characterization of pregnancy-associated maternal blood plasma enzymes and proteins, the characterization of enzymes synthesized by the placenta, and an analysis of some of the factors involved in enzyme induction in the developing fetus.

Section on Intermediary Metabolism (Gordon Guroff, Ph.D., Head). This section is involved in the development of laboratory animal analogs of mental retardation through the use of specific chemical agents and enzyme inhibitors, in the investigation of screening procedures for enzyme defects in mental retardation, and in the evaluation of the effects of excesses or deficiencies of intermediary metabolites on cellular differentiation and organogenesis. Other studies concern the biosynthesis and degradation of macromolecules in neural tissue, the transport of

small molecules across cellular membranes, and the mechanism of action of enzymes of neurochemical interest. The overall efforts of the section are to understand how changes in specific enzymes lead to changes in the behavioral patterns of the whole animal.

The Section on Physiological Controls (Walter H. Glinsmann, M.D., Head) is concerned with hormonal, neurotransmitter, and substrate regulation of cell function and biochemical differentiation. Current studies focus on phosphoproteins controlling hepatic glucose output, substrate- and hormone-dependent induction of enzymes in embryonic and adult liver, mode of action of biogenic amines, and neuroendocrine regulation of indole metabolism in the pineal gland.

Section on Developmental Pharmacology (Daniel W. Nebert, M.D., Head) investigates the macromolecular processes involved in the induction of pharmacologically important enzymes by drugs, aromatic hydrocarbons, insecticides, or hormones. This section also investigates the transplacental effects of these environmental stimuli on microsomal enzyme activity, on the metabolism of endogenous substrates in fetal tissues, and on normal fetal growth and development. *In vivo* and *in vitro* methods, including cell culture, are used to study pharmacogenetic disorders and differences in mammalian cells.

Laboratory of Molecular Genetics (Philip Leder, M.D., Chief) is concerned with the transfer and expression of genetic information. A wide variety of regulated biologic systems is under investigation, including models chosen from the areas of developmental biology, virology, cellular immunology, bacterial physiology, and bacteriophage genetics. At the present time, particular attention is being given to molecular aspects of the haematopoietic system, development of immunocompetency in cultured cells, differentiation of the embryonic chick lens, expression of the SV40 and adenovirus genomes and structural and physiologic aspects of certain RNA tumor viruses. In addition, studies in prokaryocytes are concerned with the mechanism and control of protein and RNA synthesis and with the replication and recombination of the bacteriophage lambda.

Perinatal Biology Branch. A program in perinatal biology is under development. Research will focus on a variety of studies on human and primate infants during the perinatal period and include physiology, biochemical homeostasis, and thermal adaptation.

Pregnancy Research Branch (Ronald Chez, M.D., Chief) conducts research in the physiology of pregnancy, the effects of disease states on pregnancy, and the identification of those factors which increase perinatal and maternal morbidity and mortality. At this time studies are primarily oriented toward the use of pregnant baboons, Rhesus monkeys, and sheep as models for human application. The interrelationships of fetal, placental, and maternal polypeptide hormone metabolism, tests

of placental function and reserve, and the rate limiting influences on sex steroid production during pregnancy are being examined.

The branch is beginning a clinical research program directed at the management and care of pregnant patients both as inpatients and outpatients.

Reproduction Research Branch (Mortimer B. Lipsett, M.D., Chief) conducts an integrated program of clinical, biochemical and biologic studies pertinent to endocrinology and reproductive biology. The branch accepts three Clinical Associates each year. During the first year, the associate will rotate among the Endocrinology Branches of the NIH to gain a broad knowledge of clinical endocrinology. The next 2 years are spent primarily in laboratory investigation in collaboration with a senior investigator.

The branch staffs an Endocrinology Ward and Clinic with emphasis on problems involving the pituitary gland, adrenal cortex, gonads, growth and development. Infertility clinics for men and women are also sources of patients for clinical studies. The laboratory work ranges from studies of proteins and membranes to the physiology and biochemistry of steroid and polypeptide hormones.

The Section of Molecular Structure (Erhard Gross, Ph.D., Head) carries out studies of structure and synthesis of membrane-active peptides. The synthesis of peptide hormones and collaborative studies of their actions are a focus of research.

Section of Hormonal Regulation (Kevin J. Catt, M.D., Head) places emphasis on the binding and effects of polypeptide hormones such as gonadotropins and angiotensin. Major efforts include characterization and isolation of membrane receptors and analysis of the receptor-second messenger systems.

The Social and Behavioral Sciences Branch (Leon J. Yarrow, Ph. D., Chief) engages in studies of cognitive, social, and motivational development in the early years of life. Current studies center around early environmental influences on development, and are concerned with both methodological and theoretical issues. Observational techniques are being developed to describe the early environment in differentiated, quantitative terms. Using these techniques, research in progress is on the relations between specific aspects of maternal behavior, e.g., indices of social, affectional and perceptual-sensory stimulation, and measures of infant functioning. Studies are also underway to assess early father-infant interaction. Other research is concerned with reciprocal influences in mother-infant interaction, the ways in which the infant influences maternal behavior, and how the mother-infant affectional relationship emerges.

National Institute of Dental Research

Richard C. Greulich, Ph. D., Director of Intramural Research

Edward J. Driscoll, D.D.S., Clinical Director

The National Institute of Dental Research conducts research programs in laboratory, clinical and applied science, germane not only to dental health but also to the broader interests of biology and medicine.

Physicians are appointed for a 2-year period to the Institute's laboratory or clinical programs as Research or Clinical Associates. In general, three Research Associate and two Clinical Associate positions are available annually. Specific program areas, however, will not necessarily have vacancies for Associates in a particular year.

For the most part, dentists will be appointed for 2 years as Dental Clinical Associates, with a dual commitment to research and service as described on page 2. Dental graduates who possess specialized training and interests applicable to a particular research program of the Institute may also be considered for appointment as Staff Associates, with a full-time assignment to the appropriate laboratory or branch. The number of positions of this type to be filled will be determined solely according to programmatic need.

Minimum qualification for appointment as a Dental Clinical Associate is 1 year of accredited internship, or possession of equivalent advanced training beyond the dental degree. Dentists who have recently completed specialty training will be given particular consideration. Selection will usually be made one year prior to the effective date of appointment. Thus, for example, senior dental students who will enter an accredited internship July 1, 1974, are eligible to apply for an appointment commencing in 1975.

Brief descriptions of the program areas to which Associate appointments are made are provided in the following paragraphs. Additional information about specific programs may be obtained upon request to the Director of Intramural Research, NIDR, National Institutes of Health, Bethesda, Md. 20014.

The Laboratory of Biochemistry (Karl A. Piez, Ph. D., Chief) conducts programs in basic research covering a broad range of biochemical topics. The laboratory has as its objective the investigation of fundamental biochemical processes in normal and disease states.

There are four sections within the laboratory to which an Associate may be assigned.

The Protein Chemistry Section (Karl A. Piez, Ph.D., Chief) is concerned primarily with the chemistry and structure of collagen, elastin

and other connective tissue macromolecules. Structure at the molecular level and the interactions that produce higher level tissue structure are determined by chemical and biophysical methods.

The Connective Tissue Section (George R. Martin, Ph.D., Chief) is studying the biosynthetic steps and biological regulation of collagen production. Cell culture and chemical methods are utilized to follow normal and pathological development in experimental animals and human patients with hereditary connective tissue diseases.

The Enzyme Chemistry Section (John E. Folk, Ph.D., Chief) is studying the mechanism of action of enzymes using transglutaminases as models. These enzymes produce crosslinks in fibrin during blood clotting, in hair proteins and in other biological situations. Protein chemical modification, synthesis of substrates, enzyme kinetics and characterization of the products of crosslinking are used to elucidate the important aspects of enzyme structure and its relationship to catalytic activity.

The Cell Biology Section (Herbert L. Cooper, M.D., Chief) has as its goal the determination of the important events that regulate growth and differentiation. Present efforts relate to the control of ribosome production in lymphocytes and the biosynthesis of protein in cell-free systems.

The Laboratory of Microbiology and Immunology (Stephan E. Mergenhagen, Ph.D., Chief) has as its broad objective the elucidation of the role of microorganisms and immunological mechanisms in oral and systematic health and disease. The basic and clinical programs have application to medical and dental problems and cooperative research with other laboratories is conducted as required by the interdisciplinary nature of particular projects.

Research and Clinical Associates are assigned to one of four sections according to the interest of the Associate: Cellular Immunology (Joost J. Oppenheim, M.D., Chief), Humoral Immunity (Ann L. Sandberg, Ph.D., Chief), Clinical Immunology (Reuben P. Siraganian, M.D., Chief), or Microbial Physiology (Charles L. Wittenberger, Ph.D., Chief).

The Immunology Sections are involved in studies on the role of cellular and humoral immunity in systemic and oral diseases. Current investigations include studies of the role of blocking antibodies and the effects of solubilized transplantation antigens on cell-mediated graft rejection. The contributions to cell-mediated immunity of antibody-mediated inhibition, aggregated antigen-antibody complexes, lymphocyte-macrophage interactions, and interaction of thymic-dependent and bursal-dependent lymphocytes are being studied by assaying *in vivo* delayed hypersensitivity and *in vitro* lymphocyte cultures from inbred guinea pigs, agammaglobulinemic (bursectomized) chickens, hamsters, mice, rats, and humans with a variety of disease states. In this regard, the contribution of activated lymphocytes and lymphokines to the pathogenesis of periodontal disease is being established. The isolation and

characterization of lymphokines such as chemotactic factor, lymphotoxin, and osteoclast activation factors are under intensive investigation. Studies of the biological role of the complement cascade in inflammatory responses to antigens and endotoxins, and mechanisms of histamine release in allergic as well as other antigen-antibody reactions round out the programs.

The Microbial Physiology Section conducts research on mechanisms by which growth and biochemical activities of microbial cells are regulated, with a view to explaining physiological phenomena in molecular terms. Comparative biochemical studies are directed toward resolving the means by which lactic acid production by cariogenic and noncariogenic streptococci is regulated, while other studies involve the pathways by which various organic compounds are fermented by these organisms. Mechanisms of carbohydrate transport and extracellular polysaccharide formation by oral microorganisms are also under investigation. As part of a more comprehensive approach to systematic microbiology, isofunctional enzymes of oral bacteria are being compared immunologically to determine whether their structures are similar. Using these structurally related proteins as evolutionary markers, phylogenetic relationships among oral microorganisms are being established.

The Laboratory of Biological Structure (Marie U. Nylen, D.D.S., Chief) is primarily concerned with structural parameters of normal and abnormal function as expressed at varying levels of biological organization, ranging from the subcellular to the organismic. Information is adduced from the application of biophysical and chemical methods, techniques of experimental embryology, as well as from relevant tools of modern histology.

Research and Staff Associates are appointed to the Laboratory and are assigned by mutual agreement to a preceptor in one of the following sections: Molecular Structure (E. D. Eanes, Ph. D., Chief); Experimental Pharmacology (C. T. G. King, Ph. D., Chief); Structural Interactions (H. A. Bladen, Ph. D., Chief); and Experimental Morphology (M. U. Nylen, D.D.S., Chief).

Currently, the Laboratory is engaged in a broad series of structurally oriented projects. These relate to normal growth and differentiation, drug-induced developmental abnormality, the secretory process, crystal chemistry, and mineralized tissues, as well as to morphofunctional characteristics of whole and fractionated tissue cells, macromolecules, microorganisms and viruses. Opportunities for cooperative research and training are offered in electron microscopy and diffraction, contact and projection microradiography, X-ray diffraction, infrared absorption spectrophotometry, and cytochemistry.

The Institute's Environmental Mechanisms Section and Neural Mechanisms Section execute research programs broadly focusing on oral homeostatic mechanisms in health and disease. Emphasis is currently

being placed on (1) the microbial ecology of the mouth; (2) integrated responses of the oral system as mediated by neural control; and (3) development of techniques for utilizing computer systems in experimentally monitoring and regulating the multiparametric factors which contribute to oral homeostasis. Experimental approaches derived from the disciplines of biochemistry, physiology, computer sciences and electronics play an essential role in these studies.

Specifically, the Environmental Mechanisms Section (Micah I. Krichevsky, Ph. D., Chief) investigates systems of controlled and uncontrolled interactions between a cell or group of cells and its environment. A primary aspect of these studies relates to the role of environmental cyclic or acyclic mononucleotides in cell interactions, especially those resulting in growth, chemotaxis, or structural differentiation.

Also under investigation is the response of caries-conducive streptococci to environmental parameters. Presently under study are: the dynamics of growth of these bacteria; computer-control of fermentations for studying the effect of varying physiological conditions; the nature and physiological roles of the enzymes responsible for the catabolism of sucrose; the determinants of acquisition of capability of streptococci to adhere to surfaces; and, related to this last, the dynamics of accumulation of cell-associated polysaccharides.

The Human Genetics Branch (Jerry D. Niswander, D.D.S., Chief) conducts projects in experimental, clinical, and population genetics, with the objective of elucidating the genetic mechanism in various diseases and normative traits. A variety of approaches ranging from biochemical to mathematical as well as clinical skills in both medicine and dentistry are utilized. The program of the branch is implemented by two sections.

The Development Genetics Section (Kenneth S. Brown, M.D., Chief) studies craniofacial malformations in experimental animals with emphasis on mechanisms of gene and environmental interaction in mouse strains and on development of malformations controlled by single genes. Embryological techniques are used to determine the processes of cell migration and induction that result in facial structures. Hormone and vitamin levels during pregnancy are among the variables of particular interest. Variation in human taste and smell abilities are investigated to determine the degree of genetic control of the receptor processes.

The Population Genetics Section (Jerry D. Niswander, D.D.S., Chief). Major emphasis is on family and population studies of human congenital malformations utilizing both genetic and epidemiologic techniques. Other activities involve the study of malocclusion and dental variation in different populations. Microdifferentiation in human populations (particularly American Indian groups) is also an area of concern. Investigations include the effects of natural selection and inbreeding, as well as other factors affecting mating pattern on the genetic structure

and disease patterns of different groups. A major source of data for this work is obtained from red cell and serum typing conducted within the branch.

The Neurophysiology and Anesthesiology Branch (Ronald Dubner, D.D.S., Ph. D., Chief) is concerned with the elucidation of basic mechanisms of oral-facial sensation with particular emphasis on pain sensation, and with the development and application of new methods of pain control. Fundamental research on peripheral and central nervous system mechanisms of oral-facial sensation is conducted by the Neural Mechanisms Section (Ronald Dubner, D.D.S., Ph. D., Chief). The primary objective of this research group is to correlate behavioral responses to noxious and non-noxious thermal stimuli in monkey with neuronal structure and function at various levels of the trigeminal system. A multidisciplinary approach is employed and includes the following research activities: (1) electrophysiological studies of the response of single trigeminal nerve fibers and trigeminal brain stem neurones to noxious and innocuous thermal and mechanical stimuli applied to the oral-facial region of monkeys; (2) neurocytological studies of the receptor, primary afferent, and brain stem organization of the trigeminal system in cat and monkey, utilizing light- and electron-microscope techniques; and (3) behavioral studies involving pain and temperature discrimination in monkeys trained to avoid potentially-noxious or noxious stimuli applied to the face. The NIDR Computer system is utilized for data analysis in the physiological experiments and will provide stimulus control in future behavioral, and combined behavioral-electrophysiological experiments.

Applicants for positions in this section should have special training and experience in neurophysiology, neurocytology, experimental psychology, or computer technology.

Clinical research on the development and application of new methods of pain control is conducted by the Anesthesiology Section (Edward J. Driscoll, D.D.S., Chief). The research objectives and activities of this group include: (1) physiological, pharmacological and psychological studies of the effects and efficacy of new pharmacological agents utilized in the control of pain in ambulatory dental patients; (2) the development and evaluation of methods of measuring oral-facial pain threshold and tolerance levels; and (3) the development and application of behavioral and other non-pharmacological methods of pain control.

It would be advantageous for applicants for positions in this section to have some training and experience in anesthesiology, pharmacology or psychology.

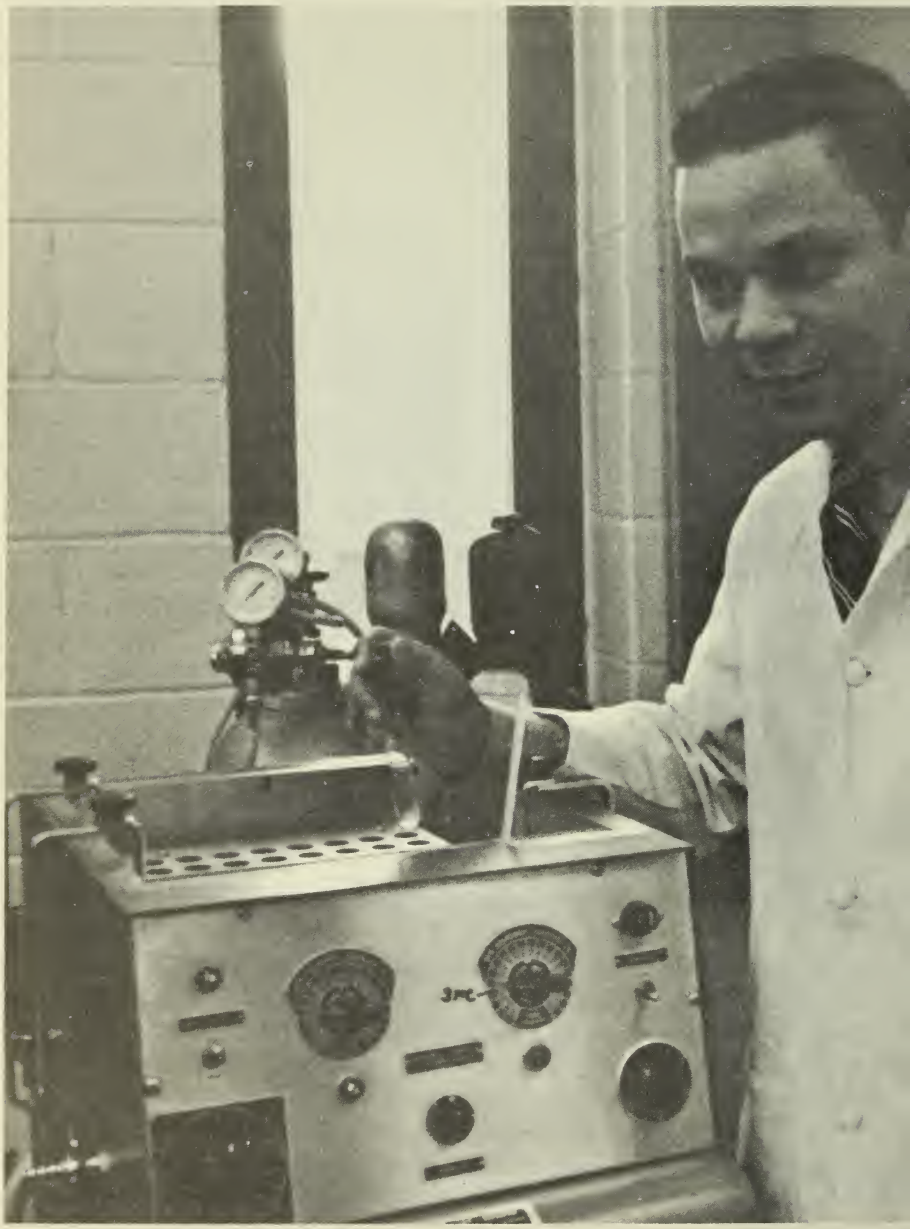
The Laboratory of Oral Medicine (Abner Louis Notkins, M.D., Chief) conducts basic and clinical research on diseases of the oral cavity. The program is highly interdisciplinary with emphasis on virology, oncology, and endocrinology. The staff includes people trained in medi-

cine, dentistry, and the basic sciences. Present research projects include factors responsible for recurrent and persistent viral infections (e.g., herpes viruses), cellular immunity in viral infections, virus-induced immunopathology, the etiology of various dermatologic disorders including aphthous ulcers, and the role of viruses and other factors in diseases of the exocrine glands (eg., Sjögren's syndrome, pancreatitis, salivary gland tumors) and endocrine glands (e.g., diabetes mellitus).

The Clinical Investigations and Research Services Branch (Richard L. Webber, D.D.S., Ph. D., Chief) provides the specialty staff and associated resources for studies, both internally and externally initiated, which are of clinical interest and/or have an interface in the Dental Clinic. A broad spectrum of research activities are encompassed, ranging from theoretical analysis of factors influencing diagnosis and treatment of dental diseases to less sophisticated investigations such as the screening of clinic patients for specific potentially pathogenic microflora. The branch is uniquely suited to such a diverse range of activity by virtue of the wide variety of interests reflected among its dentist, physician, and allied health professional personnel. In addition to direct participation in clinical research, the branch also has a responsibility for providing supportive dental care to the NIH-wide research patient population. The resulting heterogeneous distribution of dental patients provides a pool of clinical material which is unique in its capacity for both retrospective and prospective control. Current research efforts are directed toward theoretical and applied studies which capitalize on this rare combination of resources.

The Oral Pharyngeal Development Section (James F. Bosma, M.D., Chief) is concerned with investigations of the development of form and of respiratory and feeding functions in normal and in impaired infants and children. Study methods commonly include standard and cephalometric roentgenography, cinephotography, and speech recording. Basic anatomic studies are an integral part of the work of this section. Particular efforts are made to adapt familiar study techniques and therapies to patients severely handicapped by anomaly or by neurologic impairment.

The Clinical Dental Services Section (William E. Wright, D.D.S., Chief) has as its prime function the dual responsibility of providing dental care to the NIH-wide research patient population as well as of providing facilities and supportive activity to all intra-Institute clinical programs. This patient exposure provides a unique opportunity for gaining experience in the observation, treatment, and study of orofacial problems related to a variety of systemic disease. All Dental Clinical Associates are assigned to this section administratively so as to facilitate their service-related activities. However, an individual program is arranged for each Associate in order that he may also pursue effectively his clinical and/or basic research interests.



National Institute of Environmental Health Sciences

David P. Rall, M.D., Ph. D., Director

General

The mission of the National Institute of Environmental Health Sciences (NIEHS) is to identify the chemical, physical, and biological factors in the environment that can adversely affect man; to contribute to an understanding of the mechanisms and manifestations of human diseases produced by these agents; and to provide the scientific basis for the development of control measures by other agencies NIEHS is particularly concerned with the effects of agents at low concentrations acting over long periods; the interaction of multiple agents resulting in enhanced effects; and the modifying effects of variable physical and biological states within man on susceptibility to and course of disease induced by these agents.

There is no single discipline that is unique or specific for the study of environmental health problems. Rather, the distinctive requirement for such research involves the application of a spectrum of skills including biology, biochemistry, bioengineering, biometry and epidemiology, chemistry, pathology, genetics, pharmacology, physics, toxicology, and veterinary sciences.

Location

The headquarters and intramural research programs of NIEHS are located at Research Triangle Park, N.C. The National Institute of Environmental Health Sciences is the only one of the 10 Institutes comprising the National Institutes of Health to be located away from the Bethesda, Md., campus.

Proximity to three universities—the University of North Carolina at Chapel Hill, Duke University at Durham, and North Carolina State University at Raleigh—has encouraged the development of a close working relationship between the staffs of the universities and the Institute. This relationship affords the NIEHS staff access to extensive library facilities as well as opportunities to participate in teaching, in seminars, and in other scientific and professional activities associated with the universities.

Staff Associates

Staff Associates will work at the National Institute of Environmental Health Sciences under the direction of Dr. David P. Rall, Director, and

a Branch Chief in the Institute. Each Associate will work directly under a senior scientist in an area of research chosen by the Associate and the Institute.

The Pharmacology Branch (J. R. Fouts, Ph. D., Chief) studies the toxic effects on mammals of low level and/or chronic exposure to environmental constituents or contaminants. Interactions upon or within the animal of these environmental factors with each other and with drugs are also studied. Pojects currently underway include: toxication-detoxication systems in liver, lung, kidney and gut—effects of pollutants on these and the laboratory between toxication and detoxication reactions; age-related changes in detoxication systems in various organs; uptake, storage and release of chemicals in lung and liver; interaction of chemicals at sites of and kinetics of chemical distribution, storage and release—especially in the isolated perfused lung and liver, species differences in xenobiotic uptake and metabolism; marine pharmacology; inhalation toxicology—evaluation of toxicity of inhaled pesticides, solvents or aerosol spray constituents, interactions of inhaled chemicals; synthesis and release of lung lipids (surfactant and prostaglandins), incorporation of chemicals into tissue proteins and possible importance of these reactions to prolonged tissue storage or allergic reactions to chemicals; lung and cardiovascular function responses to inhaled chlorinated hydrocarbons; lung functions as detectors of inhalant toxicity; purification and comparison of components to toxication-detoxication systems in various organs.

Extensive interactions occur between Pharmacology and Toxicology and other branches for example in our program on pharmacokinetics (with Biometry), developmental pharmacology (with teratology and Environmental Toxicology) and inhalation toxicology (with Environmental Biology and Chemistry, Mutagenesis, and teratology). Interactions with Environmental Toxicology and Environmental Biology and Chemistry Branches are also involved in histologic, histopathologic, histochemical and EM studies on tissues from exposed animals.

The Environmental Mutagenesis Branch (Frederick J. de Serres, Ph. D., Chief) is responsible for the development of better methodology to test environmental chemical pollutants for mutagenic and carcinogenic activity as well as to monitor the human population to determine whether there is a change in the genetic load. In the first area, research currently underway includes investigation of the role of defective repair systems on inactivation and mutation-induction at specific gene loci, development of test systems in mammals to assay the effects of mutagens on the production of chromosome aberrations and gene mutations *in vitro* and *in vivo,* development of test systems to determine the genetic effect of airborne mutagens as well as the mutagenic effects of chemical carcinogens.

In the second area, method development is focused both on monitoring somatic mutations in peripheral blood cells and in skin fibroblasts, as well

as on the detection and measurement of germinal mutations utilizing electrophoretic serum protein variants.

The techniques utilized in the investigations include: manipulation of mutagenic and carcinogenic agents, genetic analysis of microbial organisms, cytochemistry, mammalian tissue culture, autoradiography, cytogenetics, chromatography and ultracentrifugation, and electrophoresis.

The Environmental Toxicology Branch (Robert L. Dixon, Ph. D., Chief). Scientific efforts are directed toward the understanding of mechanisms of toxicity. Special emphasis is placed on environmental problems relating to reproduction and development. These basic studies contribute to the development of better and more effective test procedures to predict toxicity in humans. Available scientific expertise is broad and includes biochemistry, reproductive physiology, pharmacology and pathology. Test Systems are likewise diverse and range from subcellular biochemistry and electron microscopy, through *in vitro* cell and organ cultures, to whole animals. Attempts are made to encourage both team and individual scientific efforts. The multidisciplinary approach is used in the general area of Ontogenesis and Reproduction which is directed by Doctor Staples, Germ Cell Development, and Basic Mechanisms of Chemical Effects on Developing Systems. Individual laboratory efforts can be defined as study of the reproductive effects of exposure to foreign chemicals during gestation, effects of foreign chemicals on oogenesis and ovarian function; passage of foreign chemicals into uterine luminal fluid and blastocyst; *in vitro* culturing of mammalian gonadal tissues; DNA repair in mouse oocytes and zygotes; study of toxic actions and effects of environmental chemicals on spermatogenesis; DNA repair by spermatogenic cells; studies to develop methods to better assess the teratologic effects of various environmental factors; comparison of local and systemic chemical treatment to induce teratogenic effects; evaluation of embryotoxicity; teratologic effects induced by heavy metals; low temperature storage of embryos and gametes; uterine luminal proteins and embryonic development; biochemical mechanisms related to the distribution and deleterious effects of environmental agents in developing systems; tissue distribution of UDP-glucuronyl-transferase during the perinatal period; factors affecting hepatic heme synthesis and hematotoxicity during fetal mammalian development; and $(Na^+ + K^+)$ ATPase behavior and plasma membranal integrity in tissues of developing animals.

Biometry Branch (David Hoel, Ph. D., Chief). The mission of the branch is to provide biometrical support for the NIEHS program by employing mathematical and statistical techniques to determine the biological effects of chemical, physical, and biological agents present in the environment. This is accomplished by incorporating in the Institute program statistical principles of experimental design, sampling, and data analysis for both laboratory and epidemiological studies, as well as mathematical analyses of biological systems. Mathematical and statistical pro-

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cedures are applied and, when necessary, developed to determine the distribution and to estimate the rates of environmentally related diseases among populations, test hypotheses and study the interactions of environmental agents from multi-factor laboratory experiments, and develop mathematical models for describing and predicting biological responses to environmental agents. The branch provides computing services for the processing of large sets of data and for the analyses of complex problems. In order to accomplish the mission of the Biometry Branch the following areas of activity are identified: (a) Analytical Statistics, (b) Statistical Epidemiology, (c) Mathematical Statistics, (d) Biomathematics, (e) Computer Programming, and (f) Data Processing.

Environmental Biophysics Branch (Lyle O. Thomas, Acting Chief) provides for NIEHS the capability of studying the impact of physical factors in the environment on man's health. Some activities are conducted in collaboration with or in response to specific requirements of other programs within the Institute. Activities of the branch include the investigation of the biological effects of physical factors alone or in combination with chemical and biological factors to which man may be exposed. Physical factors include but are not restricted to ionizing and non-ionizing radiation, heat, humidity, sound, and physical vibration. The branch is also responsible for the development and improvement of research instrumentation to support its own mission as well as the total NIEHS program.

The Environmental Biology and Chemistry Branch (John A. Moore, D.V.M., Chief) is responsible for the acquisition, quarantine, husbandry, and veterinary care of all experimental colonies used at NIEHS; maintains collaborative support laboratories in the disciplines of Chemistry, Microbiology, Pathology, Histology and Electron Microscopy, and Veterinary Medicine; and plans and conducts research appropriate to the functions of branch laboratories. Current research programs include studies on the effect of environmental chemicals on immune competence; characterization of the toxic effect of the dibenzodioxins and dibenzofurans; investigation of a variety of environmental agents such as heavy metals; and electron mass spectrometry to detect metabolites.

National Institute of General Medical Sciences

George J. Cosmides, Ph. D., Director of the Pharmacology Research Associate Program

Pharmacology Research Associates

This Institute has eight to ten positions available each year for Pharmacology Research Associates. Those who are appointed begin on July 1 and are offered 2 years of postdoctoral training in a laboratory of a participating Institute of the National Institutes of Health, under the Pharmacology Research Associate Program.

The program is directed to those who have already made a commitment in pharmacology by training or research in the field.

Associates will study principles of pharmacology and toxicology and the application of physical and chemical concepts to pharmacology. Training in such areas as applied mathematics, biometrics, organic chemistry, biochemistry, physics, and instrumentation is also available. During their tenure, Pharmacology Research Associates devote the larger portion of their time to laboratory research in the biomedical sciences, with no clinical responsibilities.

The objective of the Program is to develop leaders in pharmacology research for key positions in academic, industrial, and governmental research laboratories.

Professional growth is achieved through the process of personal guidance by senior NIH scientists who are preceptors. A variety of laboratory problems and research approaches are designed to advance both the work in progress and the competence of the prospective independent investigator. Preceptors and Research Associates are matched by a mutual selection procedure after personal interviews.

Candidates who need experience in pharmacology or who wish to broaden their experience in the biomedical sciences may make their selections from the following program areas located in the Institutes indicated below. Each of these Institutes of the National Institutes of Health participates in the Pharmacology Research Associate Program of the National Institute of General Medical Sciences.

National Cancer Institute

Laboratory of Chemical Pharmacology—Richard H. Adamson, Ph. D.

The general areas being studied include (1) the physiological disposition of antitumor agents; (2) structure-activity relationships (SAR) of antitumor agents; (3) new approaches to cancer chemotherapy and

therapeutics in general, including studies with polymers and the nature of drug receptors; (4) comparative pharmacology; and (5) induction of tumors in nonhuman primates with carcinogens and/or virus and chemotherapy of these tumors.

Chemistry Branch—C. Wesley Dingman, M.D.

Current studies in this laboratory are concerned with the interaction of those chemical and physical agents capable of inducing tumors with RNA and DNA, particularly *in vivo*. Included are studies of the effect of these agents on the metabolism and structural integrity of nucleic acids. Of special concern also are studies on the ability (or lack thereof) of mammalian cells to repair damage to DNA and its replicating mechanisms caused by carcinogenic agents.

Chemistry Branch—Harry V. Gelboin, Ph. D.

Research is being conducted on the molecular biology of microsomal enzyme regulation. Cell culture systems are used to study the mechanism of enzyme induction, the hydroxylation of polycyclic hydrocarbons, and the relationship of the microsomal enzyme system to drug action and carcinogenesis.

Drug Research and Development, Chemotherapy—Abraham Goldin, Ph. D.

The program is concerned with the investigation of the mode of action of anticancer agents. Areas of investigation include: drug action in relation of cell cycle kinetics: metabolite-antimetabolite interrelationships in chemotherapy; combination chemotherapy with reference to drug potentiation and therapeutic synergism; adjuvant and immunochermotherapy; mechanisms and therapy of tumor cell resistance to drugs; tumor invasiveness and metastasis; structure-activity relationships of antitumor agents; chemotherapy of transplantable, carcinogen and viral induced, and spontaneous tumors; molecular biological and pharmacological investigtion of the mechanism of action of antitumor agents. The laboratory program is closely related to clinical interests and an attempt is made to establish therapeutic principles for transference to clinical chemotherapy.

Laboratory of Chemical Pharmacology—Vincent T. Oliverio, Ph. D.

Studies are generally related to the pharmacological disposition of antitumor agents and other drugs in man and animals through the use of established and newly developed analytical-biochemical techniques.

Particular emphasis is placed on the study of (a) the influence of simultaneously administered drugs on the distribution, protein binding, metabolism, renal clearance, and therapeutic activity of the individual agents, (b) the pharmacokinetics of the entry of drugs across membranes into sensitive and resistant tumor cells, and (c) the carcinogenic and other

toxicological effects of drugs. Drugs of recent interest have been the folic acid antagonists, nitrosoalkylureas, substituted hydrazines, and plant alkaloids.

Laboratory of Physiology—Marco Rabinovitz, Ph. D.

The investigations in this laboratory involve the use of antibiotics and amino acid antagonists in the study of specific lesions of macromolecular biosynthesis, with particular emphasis on protein formation and its control. At times, preliminary investigations are initiated with the synthesis of proposed analogs and an evaluation of their potency and specificity. Where appropriate, different biological systems are utilized, such as microorganisms, specialized mammalian cells (e.g., reticulocytes engaged in hemoglobin synthesis) or neoplastic cells as well as cell-free preparations from these sources. In general, such studies are carried out with carbon-14 or tritium labeled amino acids and antimetabolites coupled with biochemical separation and analytical techniques.

National Institute of Dental Research

Laboratory of Biological Structure—Cecil T. G. King, Ph. D.

The section deals with the metabolism of drugs during gestation, placental transfer and how these drugs or their metabolites affect the developing embryo. Emphasis is placed on the oral facial region as it relates to the etiology of cleft palate formation and connective tissue disorders.

Laboratory of Biochemistry—George R. Martin, Ph. D.

The section is studying the formation and degradation of connective tissue and how these processes are altered in disease states. Particular attention is directed toward the metabolism of collagen.

National Institute of Mental Health

Laboratory of Clinical Science—Julius Axelrod, Ph. D.

The Section on Pharmacology is engaged in several areas of research related to biochemical pharmacology. These include studies on development of methods for the measurement of drugs, biogenic amines, and enzymes; the distribution and metabolism of drugs, the isolation and characterization of enzymes involved in drug and biogenic amines metabolism. In addition, the laboratory is engaged in examining control mechanisms of the biochemistry of the pineal gland and biological rhythms.

Laboratory of Clinical Science—David M. Jacobowitz, Ph. D.

The Section on Histopharmacology is involved with studies of monoaminergic nerves (noradrenergic, dopaminergic, serotonergic) in the brain and the autonomic nerves (adrenergic, cholinergic) in periph-

eral organs. A multidisciplinary approach is used to correlate localization of central monoaminergic nerves with function. Histochemical, biochemical and behavioral studies are currently underway. Using the catecholamine histofluorescence method, the study of drugs and stress procedures are used to observe changes in aminergic nerves. By discrete destruction of individual pathways using neurotoxic agents, correlation of various parameters of behavior is being made with regional brain neuronaly systems. Cholinergic nerves of the brain are currently being mapped out, and immunofluorescence methods are being used to study the localization of various enzymes in nerves. The growth of nerves is also studied using tissue and organ cultures.

Laboratory of Neuropharmacology—Floyd E. Bloom, M.D.

This laboratory conducts a multidisciplinary research program centered upon the identification of synaptic transmitter substances, and the mechanisms by which neuro-active and psycho-active drugs exhibit effects upon synaptic transmission. The approach is entirely at the cellular level, utilizing intracellular and extracellular electrophysiologic techniques, micromethods of drug administration including microelectrophoresis, and cytochemical studies with light, fluorescence and electron microscopy. Specifically, studies are currently being carried out on: (1) the characterization and pharmacology of potential monoamine-containing neuronal pathways in the mammalian central nervous system; (2) the relation between pharmacological responsiveness and development of structurally specialized synapses; and (3) the cytologic and physiologic organization of sympathetic ganglia.

Laboratory of Preclinical Pharmacology—Erminio Costa, M.D.

This laboratory conducts a program of research in neurochemistry and neuropharmacology to elucidate chemical and physicochemical factors involved in the clinical response of drugs affecting neuronal function. Current research includes: (1) nature of postjunctional receptors with particular regard to the biochemical reactions occurring at the neuroeffector junction in response to adrenergic neurotransmission; (2) rate-limiting enzymatic reactions controlling the dynamic equilibrium of metabolic compartments of neuronal monamines; (3) regulation of acetylcholine metabolism in synapses in relation to changes of neuron function; (4) gas chromatography-mass spectrometric assay of picomole concentrations of indolealkylamines and catecholamines in tissue and body fluids; and (5) the role of cyclic nucleotides in regulation of protein synthesis.

Laboratory of Neurochemistry—Seymour Kaufman, Ph. D.

The main effort of the laboratory is concerned with in depth studies of a group of oxidative enzymes that catalyze key reactions in the nervous system. These enzymes include phenylalanine hydroxylase, tyrosine hy-

droxylase, tryptophan hydroxlase, and dopamine P-hydroxylase. The goal is to understand the mode of fetal development, the mechanism of action, the physical structure, and the regulatory properties of these enzymes. The interaction of the enzymes with other proteins, as well as with small molecules, such as drugs and hormones, that can modulate their activities, is being studied. The regulatory properties of these enzymes are being examined at various levels of tissue organization, and include studies with highly purified enzymes as well as those with cell suspensions, tissue slices, and whole animals.

Laboratory of Clinical Science—Irwin J. Kopin, M.D.

The research efforts of the Section on Medicine are centered around the study of biochemical and physiological effects of drugs and toxins which alter the formation, disposition, metabolism and receptor interaction of putative neurotransmitters and the enzymes which control their synthesis in both the central and peripheral nervous systems. The techniques used include radioisotopic methods (*in vivo* and *in vitro*), tissue slices, perfused organs, and organ and tissue cultures.

Laboratory of Cerebral Metabolism—Louis Sokoloff, M.D.

The Laboratory of Cerebral Metabolism carries out a broad program of investigations on the biochemical aspects of growth, development, maturation, and regulation of metabolism in the central nervous system. These investigations are pursued at various levels, from molecular biology through enzymology and biochemistry, to whole animal physiology. Of particular interest are chemical compounds, such as hormones, which play important physiological roles in CNS function. Present emphasis is on the mechanism of action of thyroid hormones, not only on the maturation of the nervous system, but also on metabolic processes in all susceptible tissues.

National Institute of Arthritis, Metabolism, and Digestive Diseases

Laboratory of Chemistry—John W. Daly, Ph. D.

The laboratory is conducting research on the cyclic adenosine monophosphate-generating systems in intact brain slices; the formation, disposition and role of biogenic amines in brain and other organs; the mechanisms involved in the formation and metabolism cytoxic intermediates derived from drugs and other xenobiotics and the effects of various toxins on electrogenic membranes.

Laboratory of Biochemistry and Metabolism—Elizabeth F. Neufeld, Ph. D.

Research is in the general area of human biochemical genetics, focusing on the mucopolysaccharidoses as a model system. Cultured fibro-

blasts from patients affected with this heterogeneous group of disorders lack genotype-specific proteins required for mucopolysaccharide catabolism. These proteins can be administered exogenously to the cells, thereby causing a correction of the defect. The mechanism of action of these proteins, as well as their purification for possible therapeutic use, are currently in progress.

Laboratory of Biochemical Pharmacology—Herbert Tabor, M.D.

The work is mainly concerned with the biosynthesis, metabolism, and function of various polyamines (e.g., spermidine and spermine) and amino acids. The polyamines occur in large amounts in biological materials, and are important in stabilizing various cell components, such as cell membranes, ribosomes, and nucleic acids. Future work will be directed, in part, toward the mechanism and *in vivo* significance of these effects. The studies provide experience with a variety of techniques (e.g., enzyme characterization, bacteriophage, nucleic acid chemistry, isotopic and nonisotopic synthesis). The amino acid studies are concerned with the induced enzymes involved in histidine degradation, and their use as tools in studying induction, repression, and enzyme mechanisms. Other work in the laboratory includes studies on control mechanism, for other enzymes in bacteria and in mammalian cell culture, mechanism of action of antibiotic agents, ribosome structure, and bacterial permeability.

National Heart and Lung Institute

Molecular Disease Branch—W. French Anderson, M.D.

The Section on Molecular Hematology investigates the mechanism and regulation of hemolglobin biosynthesis. Studies include the isolation and characterization of animal and human messenger RNA for hemoglobin, cell-free protein-synthesizing systems, the mechanism of initiation of protein synthesis, RNA transcription, cell fractionation, tissue culture, and on patients. Under direct investigation are the thalassemias, hemoglobinopathies, and other types of hemolytic anemias.

Cardiology Branch—Stephen E. Epstein, M.D.

The research objectives of this branch are oriented primarily toward an elucidation of the physiological and biochemical mechanisms responsible for control of both the normal and failing heart, as well as the effects of various pharmacological interventions on the heart and peripheral circulation. Projects include pharmacologic, physiologic, and biochemical studies in man, intact animals, and the papillary muscle. Major emphasis is on the study of ten of the mechanisms responsible for arrhythmias and myocardial cell bath and acute myocardial infarction and a comprehensive understanding of the genetics and pathophysiology of various types of cardiopathies in man.

Laboratory of Chemical Pharmacology—James R. Gillette, Ph. D.

The Section on Drug-Enzyme Interaction studies various aspects of drug disposition including the relationship between drug metabolism and drug toxicity. Its main objective has been the elucidation of the mechanisms of drug metabolism by enzyme systems in liver microsomes, the factors that control the activity of these systems and the importance of these enzymes in converting inert substances to alkylating agents and other biologically active metabolites.

Experimental Therapeutics Branch—Walter Lovenberg, Ph. D.

The research of the Section on Biochemical Pharmacology is directed primarily toward understanding biochemical processes at the molecular level and how these processes function in normal and disease states. The work encompasses several fields ranging from pharmacology and clinical pharmacology to enzymology, protein chemistry, and molecular biology. Current studies are directed toward: (1) elucidating mechanisms by which enzyme levels are regulated using the enzymes of the melatonin pathway in the pineal gland which are under active diurnal regulation, (2) possible roles for vasoactive amine metabolizing systems in various disease states, (3) an investigation of possible biochemical changes occurring in various forms of hypertension.

Laboratory of Biochemical Genetics—Marshall Nirenberg, Ph. D.

The laboratory is studying problems related to neurobiology at the biomedical level using tissue culture systems.

Experimental Therapeutics Branch—Harry R. Keiser, M.D.

The Section on Experimental Medicine offers a spectrum of research opportunity ranging from basic biochemistry and pharmacology to the study of chemical factors in disease and clinical response to drugs. Major emphasis is on hypertension with studies of kallikrein-kinin system, renin-angiotensin system, prostaglandins and catecholamines conducted both in man and in experimental animals. Other current studies encompass disorders of catecholamines, serotonin and histamine biochemistry of sleep and collagen disease.

Laboratory of Biochemical Genetics—Alan Peterkofsky, Ph. D.

The Section on Macromolecules is involved in a broad program of the study of protein-nucleic acid interactions. The main system under investigation deals with the components of the protein synthetic machinery in bacterial and mammalian cells. Complexes of protein and nucleic acids are involved at various key stages in this process. For example, the mechanisms of aminoacyl-tRNA synthetases, the proteins that catalyze the attachment of amino acids to transfer RNA, are under study. The properties of the systems involved in transfer RNA modification are also an area of major interest. The enzymology of the methylation of tRNA is

related to problems of control mechanisms, differentiation, and drug action. Changes in populations of tRNA in various metabolic situations have been noted. The program also encompasses research on the mechanism of protein synthesis initiation in mammalian systems. The control of the synthesis and metabolism of cyclic AMP in bacterial cells is another area under study.

Laboratory of Chemical Pharmacology—Jerry R. Mitchell, M.D., Ph. D.

Current research concerns the study of a variety of problems in clinical pharmacology and toxicology. For example, the fulminant liver necrosis produced by commonly used drugs, such as acetaminophen and furosemide, has recently been shown to result from the formation of toxic arylating metabolites. The extent of covalent binding of these metabolites to vital tissue macromolecules is directly proportional to the severity of the hepatic damage. However, no hepatic damage or covalent binding occurs for many compounds until after the liver is depleted of glutathione, suggesting that a fundamental role of glutathione may be to protect tissues from attack by alkylating drug metabolites formed in the body. Other work concerns the cause of isoniazid-related hepatitis, the mechanisms of drug-induced hemolysis and aplastic anemia, immunologic investigations of the basic mechanisms of mixed-function oxidases, and the mechanisms of clinical drug interactions.

Laboratory of Chemical Pharmacology—Elwood O. Titus, Ph. D.

The Section on Organic Chemistry engages in projects seeking to define the interactions between drugs and the membranes of affected cells in molecular terms insofar as this is possible. Current work includes the use of physical chemical methods to study conformational changes in proteins that bind drugs, efforts to characterize individual proteins in the membrane-bound, sodium transporting system that is the target for cardiac glycosides, and radioactive labeling of adrenergic receptors in peripheral smooth muscle.

Laboratory of Molecular Diseases—Martha Vaughan, M.D.

Major areas of research interest are (1) the mechanisms underlying hormonal control of lipolysis in fat cells, with emphasis at present on characterization of the hormone-sensitive lipase and elucidation of manner in which insulin, prostaglandins and adrenal steroids affect the formation, degradation and action of cyclic AMP, and (2) the role of cyclic AMP, cyclic GMP, and compounds that influence the metabolism of these nucleotides (e.g., prostaglandins, adrenal steroids) in regulation of growth and morphology of mammalian cells grown in culture.

National Institute of Allergy and Infectious Diseases

LABORATORY OF PARASITIC DISEASES—Eugene Weinbach, Ph. D.

The effects of drugs and other toxic agents on the metabolism of mitochondria are studied to provide a biochemical basis for their pharmacological activity. Current studies are concerned with electron transport, oxidative phosphorylation, ion translocation, and structure-function relationships in mitochondria. Particular attention has been given to compounds that uncouple oxidative phosphorylation and to their mechanism of action. A hypothesis concerning the mechanism of uncoupling of oxidative phosphorylation based on conformational changes in proteins involved in energy conservation has been derived from these studies. The work will be extended to determine if other pharmacologically active agents induce conformational changes in proteins and thereby alter their catalytic function.

The Pharmacology Research Associate Committee

Choice of program area depends upon the candidate's previous training and career plans. Those who have already received adequate graduate training or conducted meritorious research in pharmacology may request as a preceptor any senior scientist at the NIH, with the approval of the Pharmacology Research Associate Committee. Since the objective of this program is to offer postdoctoral training opportunities to those interested in pursuing a research career in pharmacology, applicants without training or experience in pharmacology should select program areas which will provide such opportunities. The Pharmacology Research Associate Committee offers counseling to applicants invited to the NIH for interviews.

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National Institute of Mental Health

John C. Eberhart, Ph. D., Director of Intramural Research

Robert A. Cohen, M.D., Ph. D., Director of Clinical Investigations

This Institute offers an opportunity for post-doctoral research training in psychiatry and in the biological and behavioral sciences. Clinical Associates are assigned clinical responsibility in caring for patients who are admitted for both therapeutic and research purposes. Staff Associates engage in laboratory research in one of the biological or behavioral science laboratories under the preceptorship of one of the senior staff, and may in addition participate in tutorial seminars and other teaching programs, as their needs and desires indicate. After reporting for duty certain Staff Associates who have particular need for and interest in the tutorial seminar program, and whose qualifications are high, may be designated as Research Associates, and will be given priority in admission to the seminar programs.

Lectures, seminars, and group discussion by members of the staff and by visiting lecturers complement the training program, making it possible for all Associates to acquire a broad background in the neural and behavioral sciences with more intensive and individualized study in selected aspects of the field.

Descriptions of the NIMH program areas to which Associates will be appointed follow.

The Adult Psychiatry Branch (W. E. Bunney, Jr., M.D. Chief; Senior Staff: Dr. W. T. Carpenter, Dr. R. M. Post, Dr. Helm Stierlin, Dr. R. Wyatt, Dr. W. Pollin) conducts a broad program of research and training in clinical and biological aspects of psychiatry, including psychoanalytic studies, genetic, pharmacological and biochemical investigations of depression and schizophrenia. Ordinarily, 2 years of clinical psychiatric residency training should precede arrival on duty; for Clinical Associates, the program is accredited for third-year psychiatric residency training. Current research projects include: (1) assessment, treatment and followup of acute psychotic patients and their families; (2) biological correlates (sleep, activity, biogenic amines and related enzymes, and endocrine function) in acute schizophrenic, manic-depressive, and drug-induced psychoses; (3) mechanisms of action of psychotropic and addictive drugs; (4) clinical assessment of new psychotherapeutic drugs and treatment modalities such as acupuncture; (5) genetic studies of psychotic probands and identical twins discordant for schizophrenia and affective illness; (6) perceptual psychophysiology information theory and attention using computer and averaged evoked potential techniques; (7)

investigation of behavioral pharmacology, models of depression and schizophrenia, CNS and spinal fluid physiology and biochemistry in subhuman primates.

The Laboratory of Clinical Science (Irwin J. Kopin, M.D., Chief Senior Staff: Dr. Julius Axelrod, Dr. Philippe V. Cardon, Dr. Thomas N. Chase, Dr. Frederick K. Goodwin, Dr. David M. Jacobowitz, and Dr. Dennis Murphy) conducts a program of research in biochemistry, pharmacology, physiology, medicine and psychiatry and the interrelationships between them. Current research includes: (1) mechanism of action and metabolism of drugs and hormones which act in the nervous system; (2) biochemical studies in endocrine and metabolic disorders of amino acids, catecholamines and other biogenic amines; (3) clinical pharmacology including drug metabolism; (4) circulatory physiology and psychosomatic medicine; (5) longitudinal investigation of patients (acute or episodic psychosis, depression) stressing biological factors (endocrine function, catecholamines, serum proteins, specific enzyme activities); (6) biological rhythms and their control; (7) biological aspects of toxic psychoses and drug addiction; and (8) relationship of biogenic amines to neurological disorders, including Parkinsonism.

The Laboratory of Neurobiology (Ichiji Tasaki, M.D., Chief. Senior Staff: Robert H. Wurtz, Ph. D.) conducts research on the nervous system at several levels ranging from biochemical and biophysical studies of single excitable cells to studies of systems of neurons in the brain. Current research projects include studies on: (1) the excitation process in nerve and muscle membrane using recently developed optical techniques to demonstrate changes in birefringence, turbidity, and fluorescence in excitable tissue during an action potential; (2) biophysics of model membrane systems; and (3) the integration in the brain of visual information and extravisual input (such as eye movements and attention) using single unit recording in awake monkeys performing a learned task.

The Laboratory of General and Comparative Biochemistry (Giul'o L. Cantoni, M.D., Chief. Senior Staff: Werner A. Klee, Ph. D., Carl R. Merril, M.D., Stuart H. Mudd, M.D.) conducts investigations on: Mechanisms and pathways of protein biosynthesis; biological methylations; alkaloid biosynthesis; differentiation and gene expression in eukaryotes.

The main focus of the laboratory is on the enzymatic mechanisms in methyl transfer reactions, RNAse action, mechanism of drug addiction, muscle differentiation in cell culture, and transgenosis.

The Section on Alkaloid Biosynthesis studies the enzymes involved in alkaloid biosynthesis, their control and biosynthesis in relation to morphogenetic development of the plant; also, enzymatic mechanisms of

transmethylation and intermediary metabolism of sulfur-containing amino acids in various conditions, including inborn errors of metabolism.

The Laboratory of Cerebral Metabolism (Louis Sokoloff, M.D., Chief) conducts a program of research on: (1) chemistry of membranes; and mechanism of action of acetylcholine; (2) biochemical and immunochemical studies on myelin; and characterization of CNS protiens and their relationship in autosensitization reactions of the CNS; (3) biochemistry of the developing nervous system; (4) effects of thyroxine and other hormones on protein synthesis and on the development of the nervous system; and (5) regional cerebral blood flow and physiological and environmental factors which influence it during development of the nervous system.

The Laboratory of Neurochemistry (Seymour Kaufman, Ph. D., Chief. Senior Staff: Dr. Howard A. Nash, Dr. David M. Neville, Jr., and Dr. Audrey L. Stone) conducts investigations in the following areas: (1) the structure, mode of regulation, and mechanism of action of phenylalanine hydroxylase and the ancillary enzymes that comprise the phenylalanine hydroxylating system. In addition to studies with the pure enzymes, there is emphasis on the relationship between the properties of this enzyme system and the pathophysiology of phenylketonuria and hyperphenylalaninemia; (2) the structure and regulatory properties of the enzymes involved in the biosynthesis of norepinephrine and serotonin and the relationship between the properties of the enzymes and physiological regulation of rates of synthesis of these neurotransmitters; (3) the biochemical basis for skeletal muscle hypertrophy including the effects of exercise and neural factors in the process; (4) cell surface membrane proteins and their role in cellular differentiation; (5) DNA repair mechanisms and their role in aging; (6) the structure of viral DNA especially in relation to the phenomena of integration of viral DNA into host structures and viral transduction of host genes; (7) electronic structure of DNA and its components with emphasis on specific interactions of nucleotides in cellular processes such as codon-anticodon recognition and DNA replication.

The Laboratory of Neurophysiology (E. V. Evarts, M.D., Chief) conducts research on problems ranging from basic membrane mechanisms to brain and behavior. Current investigations include: (1) physiology and biophysics of membrane; (2) anatomy and physiology of thalamus and basal ganglia; (3) central nervous system control of movement; (4) neural correlates of learning and memory; and (5) functional role of sleep.

The Laboratory of Brain Evolution and Behavior (Paul D. MacLean, M.D., Chief. Senior Staff: John B. Calhoun, Ph. D., and Walter C. Stanley, Ph. D.) is a new facility offering opportunities for research on

evolutionary, developmental, and ecological factors relating to brain function and behavior. Large outdoor and indoor habitats are available for comparative studies on reptiles, birds, and mammals, living under semi-natural conditions. The laboratories are equipped for neuroanatomical research, microelectrode recording, brain stimulation, and psychological testing. Research emphasis is on the role of primitive systems of the forebrain in genetically constituted and species-specific forms of behavior; the influence of early experience on development; and the effects of crowding on social and individual behavior. Weekly seminars are interdisciplinary in scope, dealing with subjects of interest to workers in neuroanatomy, neurophysiology, neurochemistry, ethology, psychology, and ecology. The laboratory is beautifully located at the NIH Animal Center near Poolesville, Maryland, with open fields, a large pond for water fowl, and woodlands.

The Division of Special Mental Health Research (F. E. Bloom, M.D., Acting Director) located at Saint Elizabeths Hospital, (1) plans and conducts a program of intramural research on special mental health problems such as psychopharmacology, neuropharmacology, memory and human behavior and (2) performs clinical evaluation and followup activities in connection with research patients.

The Laboratory of Clinical Psychopharmacology (Richard J. Wyatt, M.D., Acting Chief) uses biological techniques to study both specific and generalized systems operating in the normal human brain. Chemical, physiological, and psychological behavior of these normal systems is compared to putative abnormal ones in psychiatric patients. The comparisons of normal and abnormal behaviors lead to hypotheses as to cause and possible treatments. The principal behavioral abnormality studied is schizophrenia although presenile dementia and problems of drug abuse are also investigated. The laboratory operates 3 research wards consisting of about 12 beds apiece in which a variety of pharmacological, physiological, sleep, biochemical, and psychological studies are conducted on psychiatric patients and normal volunteers. The laboratory is equipped with physiological and chemical equipment, as well as computer and animal facilities. Because of the diversity of approaches used, the laboratory seeks applicants who have both clinical and laboratory interests.

The Laboratory of Neuropharmacology (F. E. Bloom, M.D., Chief. Senior Staff: Dr. B. J. Hoffer, Dr. G. R. Siggins, Dr. F. F. Weight) conducts a multidisciplinary research program centered upon the identification of synaptic transmitter substances, and the mechanisms by which neuro-active and psycho-active drugs exhibit effects upon synaptic transmission. The approach is entirely at the cellular level, utilizing intracellular and extracellular electrophysiologic techniques, micromethods of drug administration including microelectrophoresis, and cytochemical

studies with light, fluorescence and electron microscopy. Specifically, studies are currently being carried out on: (1) the characterization and pharmacology of potential monoamine-containing neuronal pathways in the mammalian central nervous system; (2) the relation between pharmacological responsiveness and development of structurally specialized synapses; and (3) the cytologic and physiologic organization of sympathetic ganglia.

The Laboratory of Preclinical Pharmacology (E. Costa, M.D., Chief) conducts research in neurochemistry and neuropharmacology to elucidate control mechanisms involved in the clinical response of drugs affecting neuronal function. The laboratory is organized into three sections: (1) The Section on Molecular Pharmacodynamics (E. Costa, M.D., Chief. Senior Staff: S. Koslow, Ph. D., H. LeFevre, Ph. D., and J. Meek, Ph. D.) conducts studies on: (a) the molecular mechanisms of drug actions in the CNS as they affect the steady-state dynamics and metabolism of neuronal catecholamines and indolealkylamines; (b) the biochemical mechanisms that control DNA function in neurons; (c) the development of quantitative gas chromatography-mass spectrometry methods to identify drug metabolites in neurons, and to measure renovation rates of putative neurotransmitters with changes of mass due to incorporation of percursors labeled with stable isotopes (O^{18}, C^{13}); (d) the biochemical mechanisms of synaptic plasticity; (e) the assay by multiple ion detection of putative neurotransmitters; and (f) the biochemical pharmacology of cholinergic mechanisms using gas chromatography mass spectrometry (GC–MS). (2) The Section on Biochemical Pharmacology (N. H. Neff, Ph. D., Chief. Senior Staff: H–Y. Yang, Ph. D.) conducts investigations directed at: (a) measuring turnover rates of regulatory enzymes of the dynamics of putative brain neurotransmitters; and (b) identifies and characterizes enzymes controlling the metabolism of endogenous polypeptides in the brain. (3) The Section on Neuroendocrinology (A. Guidotti, M.D., Acting Chief) conducts studies concerning mechanisms of drug actions on the biochemical control of neuroendocrine integration. These studies are focused on control mechanisms for the biosynthesis of rate limiting enzymes in various neuroendocrine systems.

National Institute of Neurological Diseases and Stroke

Donald B. Tower, M.D., Ph. D., Acting Director

General. The National Institute of Neurological Diseases and Stroke conducts, fosters, and coordinates research on the causes, prevention, diagnosis, and treatment of neurological and sensory disorders and related fields, and administers a program of research and training grants and awards.

Throughout the Institute, opportunities also exist for clinical and professional education, including many scientific disciplines.

Intramural Research Program

Henry G. Wagner, M.D., Director

John M. Van Buren, M.D., Acting Clinical Director

The Medical Neurology Branch (W. King Engel, M.D., Chief) has as its major function the application of basic research techniques to the investigation of clinical neurological problems. The Clinical Associate becomes acquainted with a majority of the neurological diseases, with particular emphasis on the disorders of muscle, myasthenia gravis, lower motor neuron diseases, metabolic abnormalities of the central nervous system, and genetically determined disorders. He receives instruction in clinical neurology and the related clinical and basic sciences while developing an understanding of the various laboratory techniques which support the neurological investigation. During the first 12 months he is in a ward environment and is responsible for the care of patients on the Medical Neurology Service and the integration of related research. He covers the neurologic consultations to the other clinical services during 3 of those months. During the first year he is expected to learn to perform one of a variety of basic laboratory techniques (such as histochemistry, tissue culture, biochemistry, electron microscopy, immunology, or electromyography) as it applies to a clinical problem. The second year is spent in full-time work on that clinical research technique. Some Clinical Associates may stay a third year to continue their clinical research activities. The program is accredited for 1 year of residency training in neurology.

The Surgical Neurology Branch (John M. Van Buren, M.D., Chief) is concerned with the investigation of epilepsy, involuntary move-

ments, head injury, developmental disorders, brain tumor, cerebral edema, anatomical effects of surgical lesions on the nervous system, and psychological assessment of surgical lesions.

The Clinical Associate is required to study and has responsibility for the care of patients with epilepsy, involuntary movements, brain tumors, vascular malformations of the nervous system, and others with a miscellany of neurological disease. He receives practice and instruction in clinical neurology, and, in particular, in the diagnostic techniques of surgical neurology and the operative techniques of neurological surgery as well as the principles on which these techniques are based. He attends clinical rounds in Surgical and Medical Neurology, staff conferences in electroencephalography and X-ray diagnosis, as well as neuropathological conferences. He is advised to acquire as great a familiarity with the various laboratory techniques as is commensurate with his individual responsibilities and the commitments of the various laboratories in the NINDS.

The Electroencephalography Branch (Cosimo Ajmone Marsan, M.D., Chief) involves a relatively small highly specialized patient population from the entire Clinical Center. The position of Clinical Associate is for a 2- or 3-year appointment (preference is given to persons with basic neurological training). In neurophysiology the appointment is also for 2 or 3 years (preference is given to people with some previous experience in the field of electrophysiology and a knowledge of neuroanatomy). Current research: Experimental epilepsy, thalamo-cortical relationship, nature of brain waves, microelectrode study of cortical neurons, etc.

The Developmental and Metabolic Neurology Branch (Roscoe O. Brady, M.D., Chief; Anatole S. Dekaban, M.D., Associate Chief for Clinical Investigation). The branch is devoted to cross-disciplinary basic investigations and clinical studies of disorders of the nervous system. The research deals with (1) the pathological biochemistry, diagnosis and therapy of inherited disorders of lipid metabolism such as Gaucher's disease, Niemann-Pick disease, Fabry's disease, and Tay-Sachs disease; (2) functional abnormalities of the nervous system, including epilepsy; (3) heritable and acquired demyelinating conditions such as multiple sclerosis; and (4) the metabolism of complex lipids in tumorigenic virus-transformed cells.

The branch is comprised of the Section on Enzymology and Genetics (Dr. R. O. Brady, Head), the Section on Neurochemical Methodology (Dr. A. E. Gal, Head), and the Section on Clinical Investigations and Therapeutics (Dr. A. S. Dekaban, Head). The first two sections are primarily devoted to basic research; in- and outpatient study is included in the Section on Neurological Development.

Laboratory of Neurochemistry (R. Wayne Albers, Ph. D., Acting Chief) directs research toward the elucidation of chemical attributes of neural tissues which underlie the normal functioning of the nervous system and the derangements of function in various neurological diseases. The investigations, which are primarily at the basic level, are distributed among three sections of the laboratory: The Enzyme Chemistry Section (Head, Dr. R. W. Albers), the Section on Amino Acids and Electrolytes (Head, Dr. D. B. Tower), and the Physiology and Metabolism Section (Head, Dr. E. G. Trams). In these investigations a wide variety of disciplinary approaches and methodologies, including tissue culture and appropriate clinical material, are being utilized. Special emphasis is given to the relevance of the various laboratory programs to neurophysiological problems, such as mechanisms subserving reception, conduction and transmission of nerve impulses, and to clinical problems, such as the bases for epilepsy, cerebral edema, stroke, tumors, demyelinating diseases, and nutritional and genetically-determined disorders.

The Laboratory of Molecular Biology (Ernst Freese, Ph.D., Chief) examines the molecular mechanisms of biological processes that are affected in hereditary and viral diseases or in teratogenic effects.

In the Section on Regulation of Nucleic Acid Synthesis (Dr. R. A. Lazzarini, Head) the control of cellular and viral RNA synthesis is studied in tissue cultures. In particular, the transcription and replication of the myxo- and paramyxo- viruses is examined at the molecular level.

In the Section on Developmental Biology (Dr. Ernst Freese, Head) the transport of substrates through cellular membranes and other membrane-associated phenomena are studied in growing and differentiating bacteria and tissue cultures, as well as in isolated membrane vesicles. The inhibition of these reactions by lipophilic compounds, present in the human environment and partly known to have neurological effects is analyzed. In addition, the section determines the biochemical reason why compounds accumulating in cacogenic mutants prevent normal development or produce hereditary diseases, and it endeavors to find means of avoiding this accumulation or preventing its effect. Bacterial systems, with their powerful genetic and biochemical possibilities, are compared with human tissue cultures.

The Laboratory of Neuropathology and Neuroanatomical Sciences (Igor Klatzo, M.D., Chief) recognizes scientific advantages to be derived from close contact in the interaction between various approaches used in the fields of neuropathology and neuroanatomical sciences. Thus investigations on basic pathogenic mechanisms operative in various neuropathological conditions are carried out in parallel with or supported by studies elucidating structural and functional features of the normal nervous system. Specific problems under current investigation

are: Effects of oxygen deprivation, edema, radiation on the brain, role of the glia, development and pathology of myelin, control of carbohydrate metabolism, aspects of vascular permeability and transport mechanisms in the brain, mechanisms of neurohormonal regulation, localization of catecholamines, elucidation of some of the sensory and motor systems, investigation of neural membranes, junctional complexes, as well as the source and fate of synaptic vesicles. The main technical approaches include light and electron microscopy, freeze-fracturing, histochemistry, radioisotopic, biochemical and microchemical assays and tissue culture. The laboratory is divided into seven sections:

(1) the Section on Functional Neuroanatomy (Thomas Reese, M.D., Head),

(2) the Section on Neurocytology (Milton Brightman, Ph.D., Head),

(3) the Section on Experimental Neuropathology (Jan Cammermeyer, M.D., Head),

(4) the Section on Cerebral Vascular Pathology (Igor Klatzo, M.D., Head),

(5) the Section of Cellular Neuropathology (Henry Webster, M.D., Head),

(6) the Section on Cellular Neurochemistry (Janet Passonneau, Ph.D., Head), and

(7) the Section of Neurocytobiology (Maria Spatz, M.D., Head).

The Laboratory of Neurophysiology (M. G. F. Fuortes, M.D., Chief) conducts research on basic properties of nerve cells and on the organization of the nervous system. The *morphology* of cells, synapses and subcellular structures is studied by means of optical and electron microscopy. *Membrane properties* of receptor cells and central neurons are investigated by electrophysiological methods. Studies on *receptor functions* include analysis of the responses of visual cells to light as well as kinetic studies aimed at determining the properties of the processes leading to the response. The properties of *central neurons and synapses* are studied in simple preparations derived from vertebrates and invertebrates. Electrical and chemical properties of cells in *tissue culture* are also being investigated.

The Laboratory of Experimental Neurology (William F. Caveness, M.D., Chief) includes the following activities: (1) the investigation of the delayed effects of X-irradiation on the visual cortex of the Macaca mulatta, utilizing the visual evoked response, funduscopic photography and cerebral spinal fluid pressure, at successive intervals following exposure. Special attention is directed to (a) periodic brain swelling, and (b) retrograde and anterograde transsynaptic degeneration in the visual system; and (2) the study of development and propagation of focal seizures in the developing brain of the Macaca mulatta with the use

of electrophysiological and regional blood flow techniques. Particular attention is directed to the subcortical nuclear masses. A new effort is concerned with the delayed effects of high energy radiation to the whole brain according to clinical therapeutic regimes. The functional alterations are correlated with changes in the fine structure of the cortex and subcortical fiber systems.

One Research Associate position is available for 2 to 3 years. Previous experience in electrophysiology or neuroanatomy is essential.

The Laboratory of Neural Control (Karl Frank, Ph. D., Chief) conducts research at applied and basic levels leading to: (1) The development of neural control of external devices, i.e., outward information transfer; through the use of normal and abnormal effector organs; through detection of peripheral motor nerve fiber activity; through detection of activity of other central nervous system neurons. (2) Studies leading to the development of external control of the central nervous system, i.e., inward information transfer; through stimulation of normal and abnormal sensory pathways; through electrodes on sensory nerve pathways; through electrodes in the central nervous system. (3) Research leading to the development of neural modeling for the purpose of studying mechanisms of information processing in the central nervous system. An important part of the activities of the Laboratory of Neural Control is the exploration and development of neural prostheses through the management of contracts with outside organizations.

Applicants for Research or Staff Associate positions in the Laboratory should have special qualifications in neurophysiology, the physical sciences, mathematics, engineering or computer technology. Research experience under the guidance of an established investigator is desirable.

The Laboratory of Perinatal Physiology (R. E. Myers, M.D., Ph. D., Chief) functions within the basic neurological disciplines. Areas of specific involvement follow: (1) *Experimental Neuropathology* utilizes biochemical cardiovascular and descriptive neuropathological approaches to explore the patterning and pathogenesis of anoxic brain damage and cerebral palsy. (2) *Physiological Psychology* is concerned with the identification and characterization of neural mechanisms underlying such psychological functions as perception, memory and learning. (3) *Experimental Social Behavior*—Investigates experimental and neural bases of primate social and instinctual behavior. (4) *Developmental Neurology*—The dated monkey pregnancy program within the Laboratory enables studies within the broad area of development utilizing techniques of morphology, physiology or biochemistry.

The Central Nervous System Studies Laboratory, under the direction of Dr. D. Carleton Gajdusek, is engaged in studies of child growth and development, and slow, latent, and temperate virus infections of the central nervous system. Much of the program derives from

the study of the disease kuru and Jakob-Creutzfeldt disease, and similar subacute degenerative disorders which have successfully been transmitted to the chimpanzee and other non-human primates. The child growth study involves all aspects of the cultural and physical anthropology of native people in relation to their environment, as well as repeated medical, genetic, and microbiological examination of these intensely studied groups. Special research films are prepared on many aspects of these primitive peoples.

Collaborative and Field Research Program

Leo Fox, Ph. D., Associate Director

The goal of the Collaborative and Field Research Program of NINDS is to conduct directed research of importance and relevance to neurologic diseases and communicative disorders. The work conducted in this program is a combination of in-house and out-of-house efforts which are chiefly by means of contracts. A number of the studies underway are collaborative studies which encompass the input of a number of outside institutions. The following programs are conducted by the Collaborative and Field Research division of NINDS:

The Applied Neurologic Research Branch, under Dr. J. Kiffin Penry, is composed of the Sections on Head Injury and on Epilepsy.

The Section on Head Injury and Stroke, headed by Dr. Gaetano Molinari, conducts clinical field research targeted at control of the morbidity produced by these two major causes of disability. Investigations in progress include a prospective collaborative study of transient ischemic attacks, a study of recovery of function after head injury, and the effects of graded physical stress upon cortical microcirculation. Additional studies are planned in the area of noninvasive assessment of cerebral blood flow and prognosis for recovery after intracranial lessions. Complimenting the field program, the section maintains a laboratory for the study of the anatomical and physiological determinants of function after specific hemorrhagic and ischemic lesions.

The Section on Epilepsy is concerned with the controlled clinical studies for the evaluation of investigational anticonvulsant drugs, including their pharmacology in animals and man. This section is also deeply involved in coordinating and conducting collaborative studies of epilepsy in order to identify the consequences associated with, or developing from, this disorder; evaluating the means and the extent to which the course of the disease can be altered; investigations of the role of etiologic factors; and research to improve diagnostic and therapeutic techniques.

The Epidemiology Branch, under Dr. Jacob A. Brody, has laboratory facilities and a Section on Genetics in Epidemiology in Bethesda, Maryland, and a research center in Guam. Diseases being studied epidemiologically include multiple sclerosis, Parkinson's disease, known slow virus diseases of the CNS of man, and amyotrophic lateral sclerosis. Major efforts in genetics have been studies of dystonia musculorum deformans and acoustic neuroma. Amyotrophic lateral sclerosis and parkinsonism dementia are being intensively studied on Guam, epidemiologically, clinically, neuropathologically, and in terms of genetics, neurochemistry and a possible virus etiology.

The Infectious Diseases Branch, under Dr. John L. Sever, carries out planned directed research programs concerned with infections which damage the human nervous system. The branch is divided into three sections: (1) Immunochemistry and Clinical Investigations, (2) Virology and Bacteriology, and (3) Experimental Pathology. These sections utilize immunological techniques, serology, human volunteers and clinical trials, virology, bacteriology, mycoplasmaology, neurovirology, biochemistry, and electron microscopy, as well as experimental pathology with small animals and nonhuman primates. The program segments are: (a) perinatal, (b) acute and (c) chronic. The primary objectives are: (1) identify etiologies and improve diagnosis; (2) treatment, develop and define methods including drugs, biologicals and other methods; and (3) prevention, prepare and test vaccines and other methods.

Bureau of Biologics *

Food and Drug Administration

Harry M. Meyer, Jr., M.D., Director

The Bureau of Biologics is accepting applications for Staff Associateships in the Division of Bacterial Products, Division of Blood and Blood Products, Division of Pathology, and Division of Virology. Appointments are for a 2-year period beginning each July 1. At the end of the first year selected Staff Associates may be given the opportunity to consider continuing with the Bureau for a third year or longer. These appointments, although with the Food and Drug Administration, are for positions located on the National Institutes of Health campus.

The Bureau of Biologics has federal responsibility for the regulation of biological products. More than half of the staff is engaged in research activities interfacing with the intramural programs of the various Institutes on the NIH campus. The remaining staff members have legal and administrative skills and coordinate the Bureau's program with other FDA operations. Senior scientists in the bureau must live in both worlds in order that they can insure not only the acquisition of new research data, but its translation into effective regulatory action. Staff Associates in the bureau normally have a primary commitment to laboratory research. However, opportunities to participate in clinical investigation or be exposed to the regulatory program are usually available for interested persons. Past experience has indicated that some Staff Associates, like members of the senior staff, make contributions in all three areas.

The Division of Bacterial Products (Harold Baer, Ph. D., Director) is engaged in a program of basic and applied research in immunology and microbiology as related to bacterial vaccines, mycoplasmas, toxins, allergens, and mycobacterial and fungal antigens. Studies are being carried out in a number of areas, including: delayed hypersensitivity and tolerance; immunological mechanisms of infection and immunity utilizing whole bacterial vaccines as well as purified and characterized antigens; and measurement of the kind of antibody response. Programs will attempt to take advantage of the interest and prior experience of the applicant.

The Division of Blood and Blood Products (L. F. Barker, M.D., Director) has the responsibility for conduct of a research program relating to needs in the areas of human blood, blood components, plasma fractions and transplantation. Studies cover a broad area and involve

*Formerly a component of the National Institutes of Health.

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such disciplines as immunology, microbiology, physiology, biochemistry, etc. These include investigation of methods of tissue typing, stability of blood and blood products, and measurement of coagulation components. Persons applying for assignment to this division should be interested in studies on blood, its components, and the use of blood products in the laboratory and the clinic.

The Division of Pathology (B. L. Elisberg, M.D., Director) is engaged in a program of research in the pathogenesis of infectious diseases, hypersensitivity and immunologic responses. Animal models of infectious diseases or tumor-producing systems are studied as to the mode of transmission within the colony, spread within each animal, and the final pathologic changes that occur.

Staff Associates will receive extensive training in experimental pathology of various infectious diseases and animal tumors. In addition, there are opportunities to develop individual research projects in the area of infectious diseases and oncogenesis. Persons interested in such an assignment should have a broad interest in medicine and/or pathology.

The Division of Virology (Paul D. Parkman, M.D., Director) is engaged in a broad program of research in virology and rickettsiology. Investigators are currently working on problems involving viral vaccines, respiratory diseases, hepatitis, herpes-group viruses, tumor viruses, slow viruses, viral pathogenesis and immunology. Assignment to the division offers the opportunity to acquire a foundation in laboratory virology with experience in such techniques as fluorescent microscopy, density gradient centrifugation, cell culture techniques, diagnostic procedures and immunologic methods. For this reason the opportunity would be most valuable for persons planning academic careers in the basic sciences or clinical specialities involved with infectious diseases or related fields.

The Clinical Center

Roger L. Black, M.D., Associate Director

Jerome B. Block, M.D., Associate Director

The Clinical Center appoints Clinical Associates for the Departments of Anesthesiology, Diagnostic Radiology, Blood Bank, Clinical Pathology, and Nuclear Medicine. Associates in Anesthesiology and Diagnostic Radiology are expected to have completed their residencies prior to entrance on duty.

The Anesthesiology Department (Clarence L. Hebert, M.D., Chief) offers advanced training—through the Associate program—to medical graduates who have fulfilled residency requirements of the American Board of Anesthesiology, and who have special interest in research. (Senior residents from other hospitals are accepted for brief periods for special training. Arrangements for such assignments must be made well in advance by the director of the residency program.)

The Anesthesiology Department is organized as a central service to provide anesthesiological care for all patients hospitalized at the Clinical Center, NIH. Inhalation therapy and consultative service for special problems (respiratory, pain, etc.) are included. Opportunities exist for clinical research in conjunction with clinical duties.

Three of the National Institutes of Health have surgical services which have active programs in surgical research.

The National Cancer Institute (Surgery Branch) has a long-range program concerned with the performance of extensive radical surgery with special emphasis on the treatment of patients with malignancy of pelvic organs and structures of the head and neck. In addition, various types of other general surgery are done on NCI patients and those patients sponsored by other Institutes, who require surgery during their Clinical Center stay.

The National Heart and Lung Institute admits patients for the study and treatment of congenital and acquired heart disease. All types of cardiac surgery are performed, the majority consisting of open-heart operations performed with the aid of extracorporeal circulation. Six or more of these operations are done weekly.

The National Institute of Neurological Diseases and Stroke has several surgical programs including: localization and surgical removal of epileptogenic foci within the temporal lobe for the treatment of epilepsy; sterotaxic procedures for the relief of syndromes characterized abnormal movements and rigidity; and the removal of malignant lesions of the brain.

The Blood Bank Department (Paul J. Schmidt, M.D., Chief) is accepting applications for Clinical Associates under the matching system. Applicants with at least 1 year of training post internship are preferred.

The Department supplies over 20,000 blood products annually for transfusion to patients with unique hematologic and immunologic problems. Competent therapy is stressed and clinical programs involving the major blood components are in progress. The medical staff consists of three full-time staff physicians, and two Clinical Associates, as well as residents and medical students who are there for varying periods of training.

In addition to its service function, a significant proportion of Blood Bank activity is oriented toward clinical and basic research. As a focal point in patient care and as a repository of diverse blood samples, the Blood Bank provides a unique opportunity for collaborative research with the various Institutes. Current programs include investigations into hepatitis and the hepatitis B (Australia) antigen, the effects of biologic incompatibilities on transfusion and transplantation, immunologic studies of drug-induced hemolytic anemias, and the use of computers in laboratory medicine.

The program offers training for the clinician in the laboratory management of a patient-oriented transfusion program as well as specialized training for the clinical pathologist. A close professional liaison is maintained with the Clinical Pathology Department.

The Clinical Pathology Department (James D. MacLowry, M.D., Chief) is accepting applications for Clinical Associates whose interests lie in specialized training and research in laboratory medicine. The Department is organized into four main services: Clinical Chemistry, Hematology, Microbiology, and Data Processing. These areas are staffed by over 100 professional and technical personnel who form the operational base for the broad spectrum of laboratory diagnostic services called upon by the various Institutes for their intramural patient care programs. In addition, the professional staff of the department is engaged in collaborative and independent research in the areas relevant to laboratory medicine and the clinical diagnostic problems encountered at the Clinical Center. The department participates in the training of Residents in Clinical Pathology and interacts fully and on a professional consultative basis with the clinical programs at the National Institutes of Health.

Among the procedures and programs currently in operation in the department are automated assay systems for laboratory diagnosis, carbohydrate chromotography, amino-acid analysis, gas chromotography, radio-immuno assays, tissue culture, coagulation factor studies, and new approaches in the interface between computer assisted laboratory automation and data processing. These latter programs, in particular, are facilitated by direct access to the department's own computer facilities.

A close professional liaison is maintained with the Blood Bank Department.

A Clinical Associateship in any of the four services offers a broad experience in clinical and laboratory medicine. Each service carries on an active consultative role and participates extensively with many of the clinical services. In addition, each service provides supervised instruction in the functions of that area and opportunities are available for developmental investigation of the procedures of the clinical laboratory.

The Department of Diagnostic Radiology (John L. Doppman, M.D., Chief).

Four Clinical Associates are selected each year from among those applicants who have completed their residencies in Radiology or Diagnostic Roentgenology (Board certification not required). Such appointments are made for a period of 2 years with occasional opportunity for reappointment.

The Department is well equipped to provide the usual routine and special diagnostic radiographic examinations needed by the 27,500 patients seen each year. The preselection of patients for admission to the NIH insures a challenging and stimulating gamut of diagnostic problems.

Twelve radiologists comprise the professional staff and an adequate supporting staff is provided.

Facilities are available for both collaborative clinical and independent radiographic research projects. The development of new and more effective diagnostic techniques is encouraged and has proven possible in this program.

Close clinicopathologic correlations are made possible by frequent consultation and effective liaison with members of other department staffs.

The Department of Nuclear Medicine (Gerald S. Johnston, M.D., Chief). One Clinical Associate is accepted each year for a 2-year period of investigative clinical research. Preference will be given to applicants with prior training in Nuclear Medicine. The specific field of previous residency training is not a primary consideration, but 1 year in approved Internal Medicine, Radiology, or Clinical Pathology is recommended in order to meet the requirements for certification by the American Board of Nuclear Medicine.

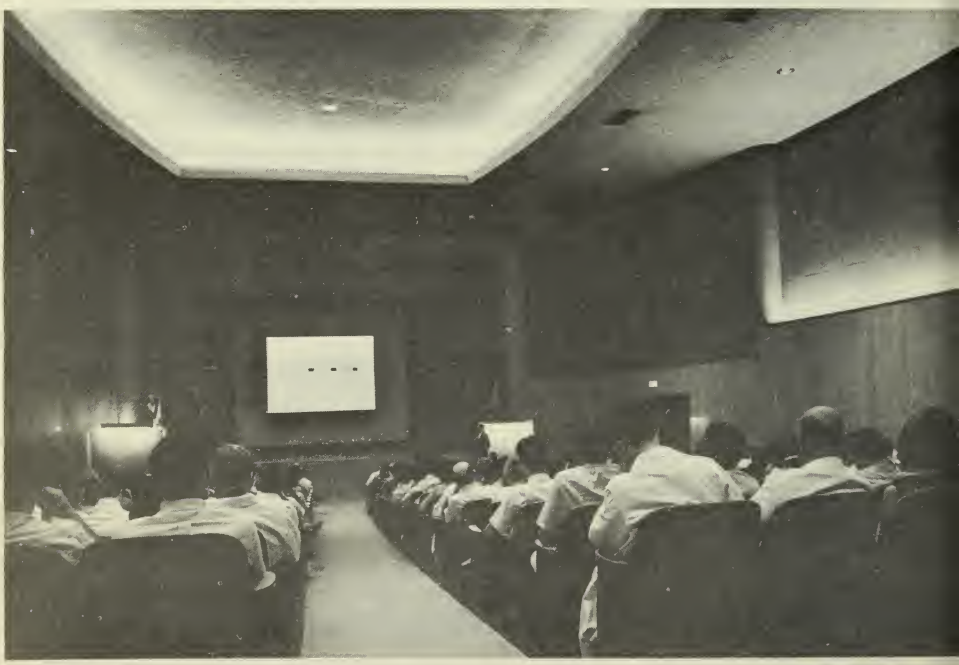
The Department consists of four sections: Diagnostic Nuclear Medicine Section, Whole Body Counter Section, Radiopharmacy Section, and Radiation Safety Section.

The Diagnostic Nuclear Medicine Section provides clinical and investigative service to the physicians of the various Institutes working within the Clinical Center. Dual probe rectilinear scanners and gamma cameras are the basic imaging devices. A dedicated computer, supported by NIH computer experts from DCRT, is located within the Section. The Whole Body Counter Section works closely with the Diagnostic Section and the

Radiation Safety Section. It operates three whole body counters and provides a consultation service to all the Institutes. It is engaged in basic research on trace quantities of radioactivity, personnel monitoring, and a variety of clinical studies. The staff of the Diagnostic and Whole Body Counter Sections consists of six physicians, a radiobiologist, a nuclear physicist, an equipment specialist, seven nuclear medical technicians, and three clerks. Departmental professionals are encouraged to interact with members of the various Institutes in order to develop new diagnostic applications of radionuclides in the investigation of a variety of diseases.

The Radiopharmacy Section employs three full-time radiopharmacists, a technician and a clerk to maintain quality control over radiopharmaceuticals used in humans as well as to compound many of the agents used by Diagnostic Nuclear Medicine. This section also provides consultations and support for the use of radionuclides in diagnosis and research.

The Radiation Safety Section provides a variety of services which include accounting for the 80 curies of radionuclides received and disposed of each year at NIH, performing calibration and safety checks on the 125 x-ray producing machines and 300 sealed sources, and surveying the 900 laboratories where radionuclides are used. There are 10 health physicists whose primary duty is to insure that NIH personnel working with sources of radiation are using safe techniques in compliance with U.S. Atomic Energy Commission regulations.



PART FOUR

Academic Programs Available to Associates

AMONG the academic programs open to an NIH Associate are: Evening courses provided by the Foundation for Advanced Education in the Sciences, Inc.; formal Seminars under the direction of NIH staff; Combined Clinical Staff Conferences; formal lectures; symposia; and an annual scientific equipment exhibit. The "N.I.H. Calendar of Events" lists an average of 25 to 30 programs each week. Other events of interest are held at universities and other institutions in the Washington-Baltimore area.

Evening Courses

Evening courses are provided by The Graduate Program of the Foundation for Advanced Education in the Sciences, Inc. Established by scientists who subscribe to the view that learning, research, and teaching are mutually reinforcing processes essential to the evolution of science, the Foundation is a non-Federal independent organization as defined by the Government Employees Training Act; however, its tuition and other fees can be paid by a Federal employer. Courses are offered in two semesters, fall and spring; courses are offered at the undergraduate and graduate levels under the programs of its several Departments of instruction: Behavioral and social sciences, biochemistry, chemistry, genetics, mathematics, statistics, physics, medicine and physiology, microbiology and immunology, languages and general studies. Further inquiries regarding The Graduate Program and requests for its current catalog should be directed to: Registrar, The Graduate Program, Foundation for Advanced Education in the Sciences, Inc., National Institutes of Health, Bethesda, Md. 20014.

Seminars

An NIH Program of formal tutorial seminars and informal discussion groups is designed in content and emphasis for prospective independent investigators, and gives them the additional opportunity to master

selected topics not adequately covered during college or graduate schooling. These exercises are an integral part of the Associate Program and are geared specifically in that direction. The program accommodates Research, Staff, and Clinical Associates and other properly qualified persons.

A number of tutorial seminars are generally made available each academic year in each of the following categories: biochemistry and genetics; mathematics and physical chemistry; cell biology, immunology and physiology.

Weekly seminars run from September through January and from February through June. Each session is of 2 to 3 hours' duration, and the participants present specific material under the direction of a qualified expert in the field. In preparation for these, the Associate does appropriate outside reading.

Combined Clinical Staff Conferences and Lectureships

Aside from the rounds and staff conferences within the separate Institutes engaged in clinical research, the Clinical Center sponsors at least one monthly Combined Clinical Staff Conference for 9 months of the year. Each conference is conducted by one of the Institute services or an appropriate Department of the Clinical Center. This series of conferences is complemented by Clinical Center Rounds which, in effect, serve the same purpose. The conferences—open to the entire clinical staff and those engaged in laboratory research as well—center around clinical case material having interest for a large portion of the staff, and serve to keep individual investigators abreast of current emphasis in all clinical research.

Several formal lectures are presented annually. The National Institutes of Health Lecture Series was established in 1953 to recognize outstanding scientific accomplishment and to contribute to the interchange of scientific information. The lectureships are awarded by the Director of NIH on the advice of the Scientific Directors of the Institutes. The R. E. Dyer Lectureship was established in 1950 by friends and colleagues of Dr. Rolla E. Dyer, Director of the National Institutes of Health, 1942–50, to pay him tribute upon the occasion of his retirement from the Public Health Service. The award is made at appropriate times—usually on an annual basis—to a scientist who has made an outstanding contribution to knowledge in a field of medical science; and is administered by NIH.

The Jules Freund lecture series was established in 1961 and is presented annually in honor of the first Chief of the Laboratory of Immunology, National Institute of Allergy and Infectious Diseases.

The G. Burroughs Mider Lectureship was established in 1968 by the Scientific Directors to honor Dr. Mider for his distinguished service to NIH. On advice of the Scientific Directors, these lectureships are

awarded annually by the Director, NIH, to a scientist who has contributed significantly to the biomedical research eminence of NIH.

Equipment Exhibit: Symposia

The NIH Research Equipment Exhibit was established in 1951 to acquaint scientists with the most modern research tools and to give them an opportunity to discuss equipment problems with representatives of industry. In 1954, a Symposium on Recent Developments in Research Methods and Instrumentation was added, offering a balanced presentation by specialists in many areas of biomedical research. The two annual events combined to provide a convenient setting for the exchange of information between research investigators and manufacturers of scientific equipment.

The NIH International Symposium on Biomedical Research was established in 1963 to emphasize the mutuality of interest of NIH and the international scientific community, particularly with the extension of NIH programs overseas.

The Washington-Baltimore Educational Complex

The Washington-Baltimore area is widely known for its educational advantages. For example, three medical schools (Howard, Georgetown, and George Washington) are located in the District of Columbia and two (Johns Hopkins and the University of Maryland) are in Baltimore. These and the universities with which they are associated, together with unique institutions such as the Armed Forces Institute of Pathology and the Naval Medical Center, offer exceptional opportunities. Some Associates find the time to pursue a certain amount of formal education at such nearby institutions.

Library Facilities

The National Institutes of Health Library (located in the Clinical Center) provides a central facility for the scientific, medical, administrative and supportive staff engaged in the NIH research program. As a self-service, open-stack library, it contains a collection of 110,000 volumes and receives annually 5,000 monographs and 3,000 foreign and domestic journals. In addition to the usual library services, the NIH Library provides on-line access to NLM's medical literature data banks, advisory services for literature needs, and a translating service.

The National Library of Medicine is located on the NIH campus. While this library serves the entire country, its proximity makes it especially valuable to NIH investigators. Holdings exceed 1 million items—books, journals, theses, pamphlets, prints, and microfilm. Researchers may consult material at the library and may request printed material through the NIH interlibrary loan service.

Addendum

Clinical Electives for Medical Students

The National Institutes of Health conducts a program of elective courses open to students from any of the nation's medical schools. For 1974–1975, the staffs of several Institutes are collaborating to supply an in-depth exposure to five clinical subspecialties: Endocrinology and Metabolism, Oncology-Hematology, Immunology, Infectious Diseases, and Clinical Psychopharmacology.

The essence of this educational experience is a close association between the student, clinical associates, and physician-scientists in several of the Institutes.

Students have patients assigned to them for workup, discussion, and participation in the pertinent studies. Special rounds and conferences are held with students. Also, students are encouraged to take part in all regular clinical and research conferences, and journal clubs.

Requests for a descriptive catalog and information concerning application for a clinical specialty elective should be addressed to:

Jerome B. Block, M.D.
Associate Director, Clinical Center, and
Chairman, Committee on Specialty Electives
National Institutes of Health
Bethesda, Md. 20014

Residency Programs

Fully approved residency programs are offered in clinical pathology, anatomical pathology, and combined clinical and anatomical pathology. Requests for information and application forms regarding these programs should be addressed to the respective program chiefs:

James D. MacLowry, M.D.
Chief, Clinical Pathology Department
Clinical Center
National Institutes of Health
Bethesda, Md. 20014

Louis B. Thomas, M.D.
Chief, Laboratory of Pathology
National Cancer Institute
National Institutes of Health
Bethesda, Md. 20014

On the basis of agreements between program chiefs and appropriate American Specialty Boards, Clinical Associates in dermatology, psychiatry, and neurology may receive credit for 1 year each. Associates in internal medicine also may receive credit toward their required 3 years of training upon application to the American Board of Internal Medicine.

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